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1847—CENTENNIAL OF THE ACADEMY—1947

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

APRIL 1947

THE EXCRETION OF WATER*

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It is well established that the renal excretion of water is in part under the control of the antidiuretic hormone (ADH) of the pituitary gland. This hormone serves to promote the reabsorption by the tubules of water from the glomerular filtrate, and to produce a minimal flow of maximally concentrated urine, the lower limits of flow and the upper limits of concentration being determined by the presence in the urine of unreabsorbed solutes, such as salt, urea, etc. It is equally well established (if frequently forgotten) that the secretion of ADH is controlled by hypothalamic centers, notably the supraoptic nuclei, and that through reflex connections with other neural centers the secretion of this hormone may be influenced by a variety of sensory stimuli, by excitement and by conditioned reflexes. Within the kidney itself, the urine flow is related, however distantly and complexly, to the rate of filtration, a renal function which is fairly static in man, but in the dog, and even more so in the rabbit, is susceptible to wide fluctuations.

Thus the rate of water excretion by the kidneys is subject to so

* This is the first of three lectures delivered under the Morris Herzstein Lectureship at the University of California and Leland Stanford University, San Francisco, California, December 2, 4 and 6, 1946.

many conditioning factors that changes in urine flow are sometimes very difficult to interpret. For over a century the rate of urine excretion was about the only thing the renal physiologist could measure, and we can sympathetically commiserate with our colleagues on their careful graphs in which V, the rate of urine flow, was plotted against T, the elapsed time of the experiment, to produce a picture that in the end was about as meaningful as a cross section of the Sierra Nevada mountains.

Against this variability in the rate of water excretion, there arise a number of major questions: How does the body keep itself in water equilibrium when water excretion is susceptible to so many disturbing factors? What factors determine the lower limits of water excretion, and why does water excretion during extreme water diuresis not rise to the upper limit set by the rate of glomerular filtration, namely, to about 130 cc. per minute, instead of rising to a maximal rate which is only about one-eighth of this value? And what do we mean by water equilibrium? What relations exist between the excretion of water and of salt, what mechanisms exist in the kidney to maintain the concentration of sodium (or total base) of the body constant and to govern the distribution of this base between chloride and bicarbonate? And how is the volume of body fluid, specifically of the extracellular fluid, regulated?

I do not presume to be able to answer all these questions, but our understanding of the excretion of electrolytes has progressed rapidly of late and I believe that it is possible at least to frame the questions with experimental data more accurately than has hitherto been possible.

In the past ten years renal physiology has passed from a qualitative to a quantitative stage, and not the least important of its quantitative advances has been the development of reliable methods for measuring the rate of glomerular filtration. We have learned that the average filtration rate in man is about 130 cc. per minute, and that out of this relatively large quantity of fluid no more than 10 or 15 per cent is ever excreted as urine, either during maximal water diuresis or in complete diabetes insipidus. Within this narrow range of 10 to 15 per cent residual water available for urine formation, variations in urine flow appear to be controlled largely if not wholly by variations in the secretion of the antidiuretic hormone. Some years ago I was led by these facts and by other evidence to distinguish what I called the 'obligatory'

from the 'facultative' reabsorption of water.[1] It was posited that the obligatory reabsorption of water, accounting for some 80 per cent or better of the glomerular filtrate, occurred in the proximal tubule in association with the reabsorption of electrolytes, glucose, etc., and that facultative reabsorption, by which variations in urine flow are effected under the control of ADH, occurred in the distal tubule. There are now reasons, which I will detail later, to challenge this view as possibly an oversimplification.

That a considerable fraction of the filtered water is reabsorbed in the proximal tubule, however, has been experimentally verified by Walker, Bott, Oliver and MacDowell,[2] who have applied the exquisite micropuncture technique, originally developed by Walker and Richards, to the study of tubular reabsorption in the guinea pig and rat. These investigators found that creatinine is progressively concentrated as the urine passes down the proximal tubule, in such a manner that by the end of this segment its U/P ratio would be about 5.0. This would mean that 80 per cent of the glomerular filtrate has been reabsorbed, leaving 20 per cent to be passed on to the thin limb of the loop of Henle and to the distal system. It is particularly to be noted that Walker and his coworkers believe that some constant fraction (*ca.* 12.5 per cent) of the glomerular filtrate is reabsorbed by each 10 per cent length of proximal tubule, so that the overall fraction reabsorbed by the end of the tubule is relatively constant and independent of the rate of filtration in the attached glomerulus. Allowing for further water reabsorption in the thin limb, it is reasonable to suppose that some 87.5 to 90 per cent of the water may be reabsorbed in these two segments, raising the U/P ratio to 8 or 10, before the urine enters the distal tubule. The maximal urine flow attainable in water diuresis or diabetes insipidus in dog or man represents roughly the complementary fraction (some 12.5 per cent), which might mean either that the remainder is reabsorbed in the distal tubule under the influence of ADH, or that an equivalent fraction fails to be reabsorbed proximally in the absence of ADH. This represents a major question into which we will inquire further.

It is known that hypertonic urine is formed only in the birds and mammals, the only classes of vertebrates in which the thin segment of the loop of Henle is present, and when Burgess, Harvey and Marshall[3] found that increased tubular reabsorption of water is induced by ADH

only in the birds and mammals, they suggested that this hormone acts on the thin segment. Since the urine becomes hypertonic under the influence of ADH, it has been generally supposed that this hormone specifically accelerates the reabsorption of water against osmotic pressure; but to assign osmotic work to the low epithelium of the thin limb, as opposed to the higher epithelium of the distal tubule, presents difficulties, and, though little has been said on the subject, I think most investigators have been inclined to the interpretation that the locus of action of ADH, and of osmotic work, is restricted to the distal tubule.

Shannon[4] has shown that the diabetes insipidus dog, in the entire absence of ADH, is capable during dehydration of elaborating a moderately hypertonic urine; one infers that ADH serves directly or indirectly, depending on its locus of action, to facilitate or accentuate this intrinsic tubular process, with the result that in the normal animal, where the supraopticohypophyseal system is intact, slight degrees of dehydration lead to a minimal excretion of a hypertonic urine, thus giving forcible control to water conservation.

In the experiments of Walker *et al*[2] the urine throughout the length of the proximal tubule remains isosmotic with the plasma, and their evidence is convincing that the proximal tubule cannot make a hypertonic urine. One important consequence issuing from this conclusion is that when any unreabsorbed substance is introduced into the glomerular filtrate (mannitol, sucrose, excess glucose, urea, etc.) it will by its osmotic pressure reduce the proximal reabsorption of water and thereby increase the load of water delivered to the distal tubule. Whether the proximal tubule can make a hypotonic urine is a matter which I think must be left open. I say this despite the fact that Walker *et al* found the urine to be hypotonic to the plasma in only two of twenty-one instances, but the conditions of their experiments—among other circumstances, the fact that most of their animals were infused with saline or sucrose before and throughout the period of observation —were perhaps not such as to favor the production of a hypotonic urine.

There is an upper limit to the maximal concentration of the urine, more or less characteristic of different species and perhaps even of different individuals, and presumably attributable to the reabsorptive capacity of the distal segment. Investigators have long searched for the factor or factors which determine this concentration ceiling; the present evidence, in which the experiments of McCance and his coworkers[5]

weigh heavily, indicates that there is but one limiting factor, and that is the osmotic pressure of the urine, whether the dominant solute is sodium chloride, sodium bicarbonate or urea. Accepting this or some modified definition of the limiting concentration of the urine, it follows that during oliguria or any other condition where ADH secretion is maximal, the urine flow will tend to increase or decrease with the load of osmotically active solutes left over after proximal tubular reabsorption, and therefore (with proper qualifications in respect to proximal tubular reabsorption) with the load of osmotically active solutes delivered to the tubules by the glomerular filtrate. Under such conditions, if glomerular activity varies the urine flow will tend to increase or decrease in a parallel manner, even though the final urine volume is only a small fraction of the glomerular filtrate. Small doses of sodium chloride, mannitol, urea, etc. will tend to increase the urine flow by increasing the distal osmotic load, and metabolic changes induced by variations in endocrine activity and the like, may through the increased excretion of sodium chloride or urea have comparable effects. I do not think such changes in urine flow, which reflect changes in osmotic load, should be called diuretic without qualification, since they have a wholly different explanation than does definitive diuresis induced by water. They could better be described as osmotic diuresis.

A second factor which has sometimes been conceived as influencing minimal urine flow is what I may call the velocity effect. Shannon[4, 6] suggested that the time during which the urine is exposed to the distal tubules may play a role in determining the amount of water reabsorbed. He utilized this interpretation in connection with the excretion of electrolytes in the diabetes insipidus dog because he noted that during osmotic diuresis induced by glucose in a dehydrated dog the osmotic pressure of the urine falls, i.e., it is only about one-sixth of the maximal value normally observed under comparable conditions of dehydration. It is as though the excess glucose discharged from the proximal tubule carried with it into the distal tubule such a flood of water that time was not available for osmotic equilibrium to be attained. However, the concentration of water in the tubules is virtually constant and maximal, regardless of the composition of the urine and the rate of urine flow, and it is difficult to see how the rate of flow *per se* could influence the amount of water reabsorbed. McCance and his coworkers have observed that sodium chloride diuresis in dehydrated rats is similarly accompanied

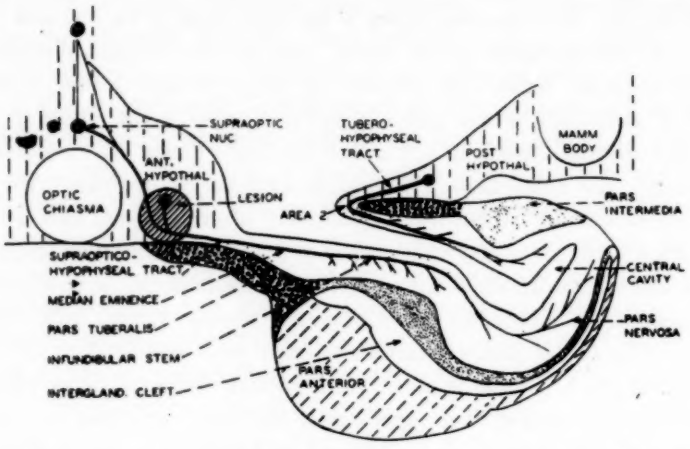

Figure 1. The anatomy of the pituitary gland in the rat. The indicated lesion is the one essential for the production of diabetes insipidus.[10]

by a fall in urinary osmotic pressure by one-half; reduction in osmotic pressure also occurs during sodium chloride diuresis in man, and more recently they have demonstrated it again with sucrose.[7, 8, 9] They suggest that the inverse relationship between urine volume and maximal osmotic pressure implies a constant quantity of osmotic work (whereby the product urine volume x osmotic pressure equals a constant) though they have not as yet presented a definitive demonstration of this relationship.

On ADH itself I need say only a few words, since the subject has been recently reviewed by Pickford[10] and Verney.[11] A considerable degree of order has now emerged from what a few years ago was a state of chaos—as Fisher, Ingram and Ranson remarked in their monograph, *Diabetes Insipidus*, "the history of diabetes insipidus reads like a comedy of experimental errors." But as a result of the studies of Verney, Pickford, Richter, White, Ranson and their coworkers, and many others, a description of the supraopticohypophyseal mechanism can now be given which will satisfy the majority of investigators. The mammalian hypophysis (Figure 1) consists of a neural division and a glandular division, the first separable into the median eminence, infundibular stem and pars nervosa, the second into the pars tuberalis, pars intermedia and pars anterior. The so-called posterior lobe, a term which

Fisher *et al* discard because of its ambiguity, is made up of the pars nervosa of the neural division and the pars intermedia of the glandular division. It is in the pars nervosa that ADH is elaborated. The pars nervosa receives nerve fibers from perhaps several hypothalamic nuclei, but chiefly from the bilateral supraoptic nuclei, which nuclei give their name to the supraopticohypophyseal tract. Any circumstance, and only such circumstances, as will destroy bilaterally the supraoptic nuclei or interrupt the supraopticohypophyseal tract, or destroy the neural tissue of the infundibular stem and median eminence as well as the pars nervosa, will wholly destroy the capacity to secrete ADH; in the absence of this hormone (except in marked dehydration, when the intrinsic activity of the distal tubules comes into play), the urine flow rises to the limit set by 'obligatory' reabsorption (we return the word to quotation marks since it must be used tentatively); i.e., to about ⅛th of the glomerular filtrate, or in man to some 16 cc. per minute or 23 liters per day. Such is the circumstance in experimental diabetes insipidus and such is essentially the condition during maximal water diuresis, when secretion of ADH is in abeyance. In water diuresis, as in diabetes insipidus, in the dog and in man, there is no *necessary* change in the filtration rate or renal blood flow[11-18]—the whole matter concerns the reabsorption of that residue of water left over from the 'obligatory' process.

ADH is distinct from the oxytocic and amphibian water-balance principles, which are secreted by the neural division, and from the melanophore principle, which is secreted by the pars intermedia.[19] It occurs in all classes of vertebrates[20] though only the mammals and to a lesser extent the birds can elaborate a hypertonic urine.

ADH is immediate and constant in its action, which is best revealed by the arrest of diuresis following a standard dose of water in a well hydrated animal. Administered intravenously its effects wear off in 30 to 40 minutes. Its essential mode of action is the direct effect upon the reabsorption of water by the renal tubules, an effect which is quantitatively related to the logarithm of the dose.[21] The increased excretion of chloride, long associated with ADH, is probably attributable to small quantities of pitocin in commercial preparations;[16, 22, 23, 24] the choluretic action of pitocin itself is possibly not a specific effect upon chloride reabsorption in the tubules but referable to changes in filtration rate. Minimal urine flow in hydrated dogs is obtained by the intra-

venous administration of about 5.0 milliunits per hour, a dose far smaller than is usually used by experimentalists, but true minimal urine flows are obtained only by a combination of dehydration and hormone secretion—for in the latter condition the filtration rate is decreased, thus decreasing the delivery of electrolytes and water to the proximal and hence to the distal tubule.[4-6]

Most investigators agree that the normal stimulus inducing secretion of the antidiuretic hormone is an increase in the osmotic pressure of the plasma,[25, 26] but whether this acts upon the supraoptic nuclei or on other neural centers is not determined. Verney's[11] recent experiments indicate that the osmoreceptors are reached by the internal but not the external carotid artery. The supraoptic nuclei, it may be re-emphasized, have such far-flung connections that a large variety of stimuli can influence neurohypophyseal secretion.[11, 27, 28] Ether and chloroform anesthesia induce increased hormone secretion, either by a 'release' phenomenon or by stimulating the supraopticohypophyseal system; morphine is particularly potent in this respect and all the barbiturates are in some degree effective.[29-32] It was the use of anesthetized animals that led Magnus and Levy, who first studied the effects of pituitary extract on urine formation, to assert, falsely we now know, that such extracts have a diuretic action. I would not labor these points were it not for the fact that there is still evident a tendency to attach unwarranted significance to changes in urine flow, to base upon such changes the alleged discovery of a new hormone, or a new specific inducing tubular diuresis, or, without recourse to readily available measurements, to infer from them changes in filtration rate.

I have thus far discussed the factors, so far as they are known, which determine the upper and lower limits of water excretion within the bracket of 'facultative' reabsorption, i.e., throughout the course of water diuresis. Osmotic diuresis presents a somewhat different problem and cannot be resolved without better knowledge of the excretion of electrolytes and of the relations between proximal and distal water reabsorption.

We may now turn to the meaning of water equilibrium. The most fundamental consideration here is the fact that water moves freely between all parts of the body, by way of the circulating plasma, and distributes itself in such a manner that the effective osmotic pressure of the three major osmotic compartments of the body, the plasma, the

extracellular (or interstitial) fluid compartment and the intracellular compartment, is the same except in so far as differences are maintained dynamically by differences in hydrostatic pressure or tissue pressure. However, the mere fact that water is, in the osmotic sense, uniformly distributed throughout the body does not place any limitation upon the actual volume of water, or of isotonic fluid, contained within any one of these three compartments, since the number of osmotically active constituents in each can and does vary more or less independently. Between the extracellular fluid and the plasma water moves in accordance with the balance of forces between the hydrostatic pressure of the blood in the capillaries and the oncotic pressure of the plasma proteins. Between the extracellular fluid and the tissues, water moves along gradients determined largely, if not entirely, by osmotic forces. Water and electrolytes are always being added to the body or subtracted from it, moving from plasma to extracellular fluid or in the reverse direction, as the organism departs from or approaches equilibrium.

In the extracellular fluid, the principle osmotically active constituent is sodium chloride, though more exactly we should speak of the total base with its chief attendant anions, chloride and bicarbonate. The constancy of the total base and its physiological significance in body fluid regulation have been recognized ever since Gamble, Ross and Tisdall[33] reported on this subject nearly 25 years ago, and it is to be regretted that in recent years it has received scant attention. Opposed to the osmotic activity of these non-penetrating electrolytes is the osmotic activity of the tissue electrolytes, chiefly potassium and magnesium. The concentration of the intracellular constituents, which seem to be fairly rigidly confined, is presumably determined by the cellular protein which gives to the cell its fixed characters. It seems probable that it is the quantity of osmotically active material in the cell which constitutes the point of reference in the regulation of the osmotic pressure of the extracellular fluid.

It has been said that the effective stimulus to the osmoreceptors of the supraopticohypophyseal system appears to be the osmotic pressure of the extracellular fluid. It seems probable that the osmotic pressure of this fluid is significant primarily in reference to the more stable osmotic material in the cell. In this view, the maintenance of intracellular osmotic pressure is the crux of water regulation. When the required intracellular osmotic pressure is attained, specifically in these osmoreceptors,

water equilibrium is reached. (This view does not allow for the slow exchange of electrolytes or of other osmotic constituents between cells and the extracellular fluid which may lead to adaptation, or for diffusion gradients and other secondary factors, and must be looked upon as a tentative and skeletonized statement.)

Water equilibrium can be attained at any volume of the extracellular fluid, large or small, and we are therefore forced to believe that a mechanism exists for the conservation or excretion of total base, and particularly sodium, which operates more or less independently of the mechanism for conserving water, and specifically in relation to the volume of the extracellular fluid, for otherwise the quantity of sodium in the body, and hence the volume of extracellular fluid, could expand or contract indefinitely.

Before we seek to explore this question further, however, let us recall that in the renal conservation of water, there is a division of labor between the proximal and distal tubule. It is to be anticipated that in the renal reabsorption of electrolytes a similar division of labor will throw the bulk of reabsorption on the proximal tubule. Proximal reabsorption may be looked upon as a sort of internal circulation within the kidney which stems from the glomerular filtration-tubular reabsorption pattern of that organ, and which has nothing to do with the finer control of water and electrolyte conservation.

But upstream to the renal tubule is the glomerulus, designed to pour both water and electrolytes into the nephron in a flood which is quantitatively out of all proportion to the needs of the organism to excrete either. I never cease to marvel at the extravagance of this operation: in man the water filtered per day amounts to some 180 liters, or more than three times the total body water, of which only one or two liters are excreted; the total sodium chloride filtered amounts to nearly 1200 grams, of which only some 5 to 10 grams are excreted; the total sodium bicarbonate amounts to some 400 grams of which only 200 mg. are excreted. The ratio of filtration to excretion is thus roughly 100, 200 and 2000 to 1, a proportion which warrants the use of the term extravagant.

Apart from the fact that the process of urine formation starts with this seemingly superfluous flood of water and electrolytes requiring tubular reabsorption, what specific role do the glomeruli play in water and electrolyte balance? In the frog the administration of water is ac-

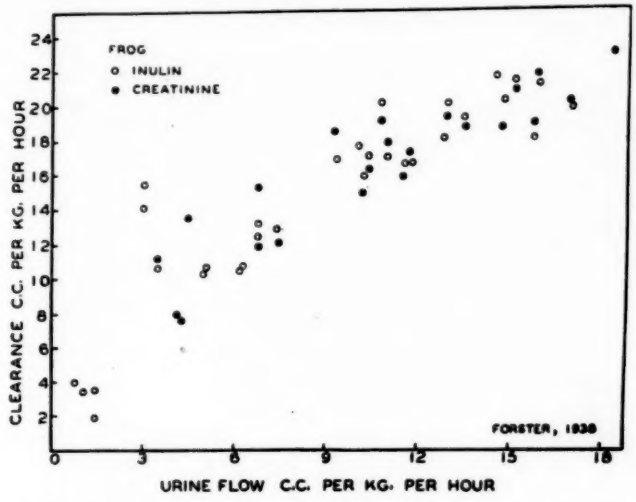

Figure 2. Relations between glomerular filtration rate and urine flow in the frog.[34]

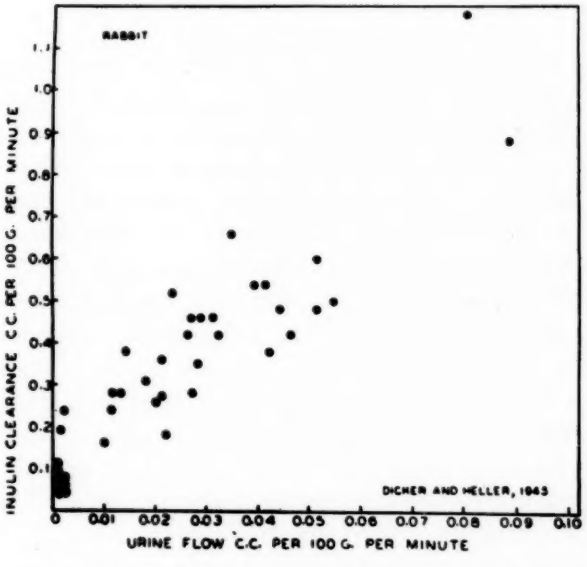

Figure 3. Relations between glomerular filtration rate and urine flow in the rabbit.[35]

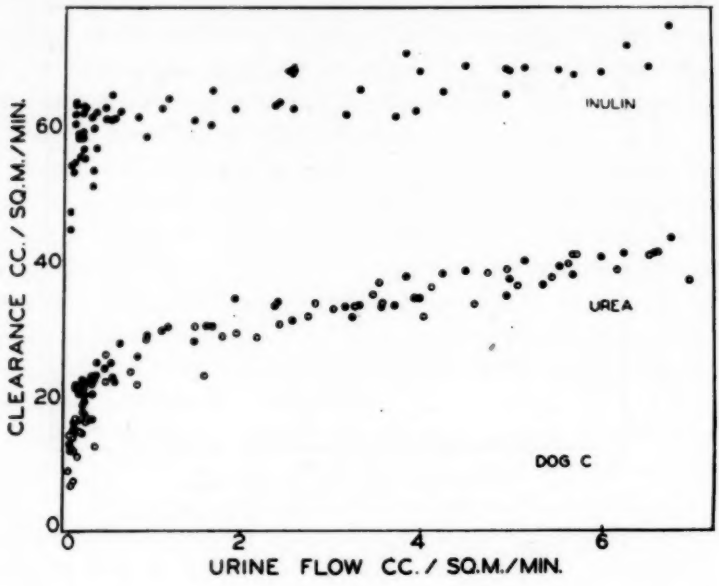

Figure 4. Relation between glomerular filtration rate and urine flow in the dog.[31]

companied by a marked increase in the filtration rate (Figure 2); by the glucose saturation method, Forster[34] has shown that this increase in filtration rate is attributable to an increase in the number of active, or fully active, glomeruli. During oliguria glomerular activity is reduced to a very low level. One may suppose that variable glomerular activity represents a primitive method of regulating the urine flow, and hence water excretion, since the antidiuretic hormone accelerates the tubular reabsorption of water only in the birds and mammals, the only forms in which a hypertonic urine is formed.[3] Whether this relationship is primitive or not, it is strikingly evident in the rabbit, which behaves almost like the frog in that hydration provoking an increase in urine flow is accompanied by an increase in filtration rate[35, 36, 37] (Figure 3). With the possible exception of the marine seal, which has not been carefully examined with respect to water diuresis, the rabbit is the only recorded mammal that shows this phenomenon.

(It is worth noting parenthetically that the recent report of Trueta and his colleagues[38, 39] on the continued perfusion of the renal medulla

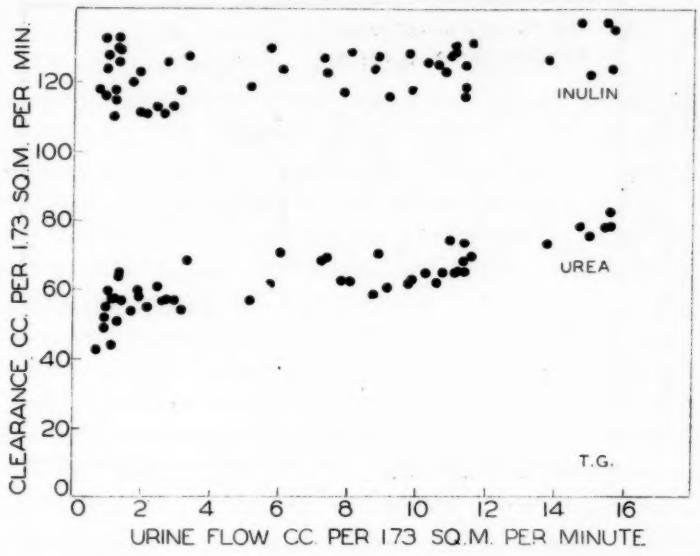

Figure 5. Relation between glomerular filtration rate and urine flow in man.[13]

during cortical ischemia produced by tourniquet shock is apparently based solely on rabbits (the species is not named but rabbits are designated in their preliminary report), and if such is the case the observations need to be confirmed in other species. With the glomerular circulation in the rabbit so labile, it is possible that *vasa rectae* and other glomerular by-passes are of greater importance in this species than in other animals.)

In the dog, however, the filtration rate is essentially independent of hydration except at extremes of dehydration or excessive hydration[7] (Figure 4). Yet it is well demonstrated that glomerular filtration is a relatively labile function in the dog: it can be reduced by severe dehydration,[4, 6] and increased in normally hydrated animals by 50 per cent or more by the administration of saline,[4, 6, 40] saline possibly being more effective than water in this respect because water is distributed throughout the body tissues, whereas saline is confined to the extracellular compartment. Shannon inferred that these changes in glomerular activity reflect and probably are initiated by changes in the volume of the extracellular fluid, an inference that does not exclude reduction of the

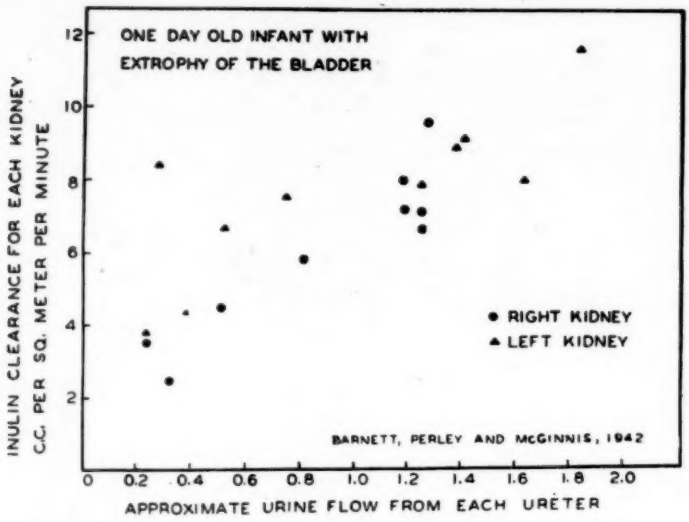

Figure 6. Relation between glomerular filtration rate and urine flow in a one-day old human infant.[48]

oncotic pressure of the plasma proteins, or in viscosity by dilution of the red cells, as factors that will increase the effective glomerular pressure. The overall magnitude is such, however, as to indicate that the glomerular apparatus itself is involved. The dog also shows a substantial increase in filtration rate on a high protein diet, and a substantial decrease on a low protein diet,[41, 42] the effects of protein being imitated by amino acids and certain other metabolites.[43] Here the changes in glomerular activity are certainly mediated by the glomerular-vascular apparatus.

Dicker and Heller's[36] report on the rat shows that in respect to hydration this animal resembles the carnivorous dog, rather than its rodent cousin, the rabbit. Why these species differences exist remains a puzzle and more studies in comparative physiology are needed to clarify this important problem.

Even more stable than in the dog, the filtration rate in the adult human kidney (Figure 5) is not specifically related to hydration[12] and changes only moderately after the administration of saline[44] or during excessive dehydration.[8, 45] As judged from the urea clearance, it changes very little with changes in the protein content of the diet,[46, 47, 48] al-

though children are more susceptible to protein intake.[49] In respect to hydration, however, young infants behave like rabbits, the filtration rate increasing markedly with urine flow[50-53] (Figure 6). This functional relationship appears to be associated with the inactivity of the glomeruli during fetal life, and we need to know more about the specific adaptations peculiar to placental reproduction before we can think of it as primitive and harkening back to our tadpole ancestry.

I want to emphasize here, not the relative stability of the filtration rate in the adult human, but the fact that it can and does vary under conditions not yet defined. This variability is much greater in the dog, and most remarkable in the rabbit. The fact of this variability immediately raises questions concerning glomerular-tubular balance, for it is now well established that in many instances the reabsorptive capacity of the tubules is sharply limited. Such limitations have been demonstrated (in the dog or in man) in the tubular reabsorption of glucose,[54, 55] phosphate,[56] amino acids,[57] creatine,[57, 58] and vitamin C.[59, 60] In each of these instances, however, the plasma concentration of the substance in question is determined by equilibria between the plasma and some organ other than the kidneys (the liver, in the case of glucose and amino acids, the bones in the case of phosphate, etc.), the kidneys serving only as a retaining dam to prevent wasteful excretion at normal plasma levels; only at elevated plasma levels is the tubular reabsorptive mechanism saturated and the excess glucose, phosphate, creatine, etc. allowed to escape from the body. The role of the kidneys here is merely one of a safety valve. Moreover, the maximal rate of reabsorption of the substances named is, with the possible exception of phosphate and creatine, of such an order of magnitude that, at normal plasma levels, an increase in the filtration rate within the normal range does not impose upon the tubules a load in excess of their reabsorptive capacity and the filtered material remains completely or almost completely conserved.

The situation is, however, very different with electrolytes. There is no credible evidence that any organ in the body can store sodium chloride or sodium bicarbonate, or can secrete them or otherwise participate in the regulation of their plasma concentration. Setting aside secondary disturbances (water and electrolyte shifts between the plasma and tissues, the secretion of the enteric fluids, etc.), the regulation of the plasma concentration of these electrolytes is solely and continuously a renal responsibility, as much as it is in the case of water. Clearly, if

the renal tubules are to be charged with conserving or rejecting some small fraction of the filtered sodium chloride and sodium bicarbonate, the absolute magnitude of the filtration rate will be a matter of great importance.

Summary

The reabsorption of water by the renal tubules may be divided into two clearly separable processes which, until better terms suggest themselves, may be called the obligatory and facultative processes. Obligatory reabsorption accounts for some 80 to 87 per cent of the glomerular filtrate and most of this may be referred to the proximal tubule, while facultative reabsorption accounts for the remainder.

Facultative reabsorption is under the control of the antidiuretic hormone (ADH) of the neurohypophysis. Whether facultative reabsorption is to be referred to the distal tubule or the thin limb of the loop of Henle remains open to question, but it is within this bracket that variations in urine flow must be adjusted to keep the body in water equilibrium. The maximal urine flow in water diuresis or diabetes insipidus cannot exceed the facultative fraction (some 13 per cent, at a minimal U/P ratio of 8) of the filtration rate. The minimal urine flow is conditioned by the load of water and osmotically active solutes delivered to the distal tubule, the precise osmotic limitations on distal water reabsorption being unknown.

The secretion of the antidiuretic hormone from the neurohypophysis is under the neural control of the supraoptic nucleus. The effective stimulus eliciting an increased secretion of this hormone is an increase in the osmotic pressure of the blood. The osmoreceptors, as yet unidentified, are probably located in the central nervous system. The action of the antidiuretic hormone, so far as positive evidence is available, is confined to the promotion of water reabsorption by the renal tubules.

Water moves freely between all the fluid compartments of the body, and water equilibrium is apparently attained when the osmotic pressure of the extracellular fluid is balanced against the fixed osmotically active constituents of the osmoreceptors of the neurohypophyseal system. Water equilibrium can be attained at any volume of the extracellular fluid, and the control of the volume of the extracellular fluid is a problem distinct from the conservation of water itself.

Glomerular activity, which determines the supply of water and electrolytes to the renal tubules, is intrinsically variable, though the degree of variation differs markedly in different species, as well as between the infant and the adult. Since the renal tubules are solely responsible for the retention of both water and electrolytes, the maintenance of an appropriate balance between glomerular and tubular function is a matter of considerable importance in the problem of body fluid regulation.

(To be continued)

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PHARMACOLOGY OF STREPTOMYCIN*

HANS MOLITOR

To most clinicians streptomycin meant as recently as one year ago scarcely more than another antibiotic with theoretically interesting properties; today, however, this agent has advanced to a position second only to that of penicillin. With the difficulty of large volume production already overcome and ample supplies freely available, it is safe to predict that in the physician's armamentarium this drug will soon become a tool of first importance.

Any drug, which is reasonably safe and possesses activity against such common diseases as tuberculosis, E. coli and Salmonella infections, is bound to be widely tried. There are probably only two obstacles which at this moment may keep streptomycin from being used in far more cases than justified on the basis of present evidence: its cost and the necessity of frequent administration by the parenteral route. With streptomycin, as with penicillin, the initial cost of the product was of necessity high. However, with improvements in production methods the cost has already been materially reduced and it seems not unreasonable to expect that this trend will continue; and as far as the mode of administration is concerned, it is hoped that by improvement in the pharmaceutical forms of the drug the inconvenience of repeated parenteral administration may be surmounted, similar to the development that has taken place with penicillin.

In view of the anticipated wide use, it seems therefore timely to present a description of the pharmacological and toxicological properties of streptomycin, particularly since in its presently available form this drug may cause certain undesirable side-reactions.

At the onset, I should like to state that the information given today is somewhat different from that believed to be correct one or two years ago. Having participated in the pharmacological study of streptomycin since its very beginning and having presented the results of such

* Presented at the Stated Meeting of The New York Academy of Medicine, December 5, 1946.
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studies on several previous occasions, I have become particularly aware of these changes. To give you a brief example: In May 1945, in one of the first reviews of the pharmacology of streptomycin, nausea, headache, flushing of the skin and occasional fainting spells were listed as the most common side-reactions; in January 1946,[1] the statement could be made that these effects were due to an impurity which in the future would be removed in the process of manufacture. Mention was made at that time, however, of another, and more serious, side-effect, consisting of disorders in the vestibular and auditory system. These effects, first observed in man by Hinshaw and Feldman[2] and in animals by our group, were then believed to be an intrinsic property of streptomycin. Now it has again become necessary to modify these views.

These frequent changes lie not in faulty experiments or a hasty interpretation of the results, but rather are due to the fact, that the drug available today is quite different in purity from that supplied experimenters one or two years ago.

These differences, however, manifest themselves only in a change of the toxicological reactions and do not effect the chemotherapeutic properties. Therapeutic results obtained with a given number of streptomycin units of one of the early preparations, which rarely exceeded a purity of 25 per cent in terms of the active principle, are reproducible by the same number of streptomycin units of one of the later batches, which are 70 to 95 per cent pure. There are, however, very definite variations in the type, frequency and severity of side-reactions observed with samples of different purity.

Like penicillin, streptomycin at the time of its discovery and first investigation was a rather crude mixture, containing in addition to the active principle a multitude of contaminants, some of them inert, others pharmacodynamically highly active. While the absolute quantity of these impurities varied with individual batches, their qualitative properties remained essentially the same, as long as the conditions of manufacture were not changed. In view of this it was permissible to speak of "standard" impurities, to be expected in all commercial preparations of a similar type of manufacture; indeed, the specifications of the Food and Drug Administration recognized the presence of these impurities, and permitted their presence up to a certain, moderate degree. The latter provision was made because a complete exclusion of some of these frequent contaminants would, at that time, have reduced the

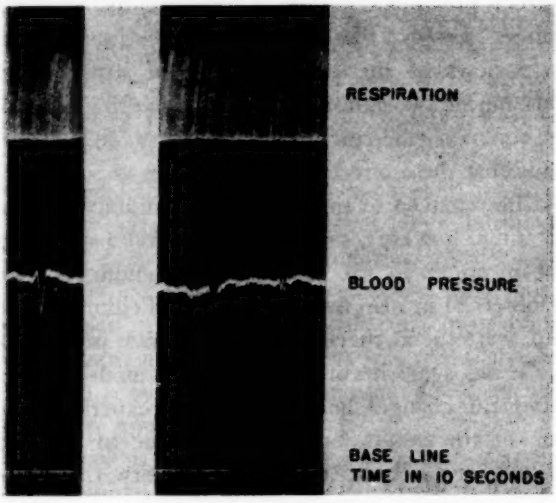

Figure 1. Blood pressure effect before and after histaminase treatment. Cat 3.25 kg. nembutal anesthesia 35 mg/kg. subcutaneously.
1. **Histamine hydrochloride 1.00005 mg/kg.**
2. **Streptomycin concentrate lot 206, 50 units/kg.**
3. **Streptomycin concentrate lot 206, histaminase treated, 50 units/kg.**

output of the much needed drug too severely. Side-reactions described in the earlier clinical papers need therefore not necessarily be expected with today's preparations, even though the therapeutic claims remain unaffected. Indeed, because a several-fold larger dose of streptomycin preparations of greater purity may be administered with impunity, it is possible to obtain today favorable results in cases where the use of one of the earlier streptomycin preparations might have failed, due to limitation of the maximum tolerated dose.

Among the pharmacodynamic effects that can be produced in animals by the administration of excessive doses[3] and that are partly due to impurities, are the following:

1. *Circulatory Effects.* These were histamine-like and consisted in animals of peripheral vasodilatation, fall of blood pressure, increased secretion of gastric juice, temporary inhibition of water diuresis and contraction of the isolated intestine and uterus. Since histaminase, an enzyme specifically destroying histamine, abolished these effects, they

must be ascribed to an impurity closely related to, or identical with, histamine. This impurity has now been completely removed, at least in the material examined in our laboratory (Fig. 1).

In man, this impurity was responsible for such reactions as headache, nausea, vomiting, reddening of the skin, and occasionally, fainting spells, which occurred not infrequently with the early, impure material, particularly when it was injected intravenously at a rapid rate. It was found that the incidence of these reactions in man was proportional to the blood pressure lowering effect of the same lots in animals and it seems therefore reasonable to expect that with the elimination of this impurity the occurrence of clinical side-reactions of this nature has become a matter of historical interest only.

2. *Hepatic Changes* consisting in fatty metamorphosis and degeneration, may be produced in animals with very large doses. No such changes have been observed in man.

3. *Renal Effects* such as albuminuria, hematuria and appearance of casts are due to glomerular and tubular degeneration and necrosis; they are reversible, if administration of the drug is stopped in time. In man, severe effects of this nature have been observed only with one of the earliest samples; however, an appearance of casts, without albuminuria, does not seem to be infrequent, particularly when the urine is acid. It has been, however, transitory and not of serious consequence, in any instance thus far recorded.

The renal and hepatic effects of streptomycin depend largely upon the purity of the sample used, but even highly purified material may produce them in animals provided extremely large doses are given.

4. *Neurotoxic Properties.* Hinshaw's original observation of a labyrinthine disturbance in patients repeatedly receiving large doses of streptomycin has been confirmed by other clinical investigators. The use of accurate tests for vestibular and auditory function has shown, that it is more frequent than was originally assumed, for patients quickly learn to compensate for the vestibular dysfunction and notice its presence only when blindfolded or in the dark. The auditory effect, which apparently requires still larger doses of streptomycin, may result in a marked loss of hearing, particularly for the high frequencies. The vestibular effect can be produced in dogs and rabbits and persists for a long time after discontinuation of treatment. It may become irreversible if the streptomycin administration is not terminated.

TABLE I—COMPARISON OF DOSES NECESSARY TO PRODUCE NEUROTOXIC SYMPTOMS

Influence of Mode of Administration on Dose and Time Required for Neurotoxic Signs

	Route	*Units Per Kilogram Per Day*	*First Appearance of Neurotoxic Signs*	*Total Dose Units per kg.*
Dogs	I.M.	100,000	20 Days	2,000,000
	I.C.	1000 (1 Dose)	Within 1 Hour	1000
Rabbits	S.C.	300,000	11 Days	3,300,000
		450,000	7 Days	3,150,000
	I.C.	1000-1250 (1 Dose)	Within 1 Hour	1000-1250

In animals the neurotoxic reactions were first produced by repeated intramuscular injections of large doses (100,000-200,000 units per kg.). The relatively long interval of 1 to 2 weeks between the administration of the first dose and the appearance of vestibular dysfunction made it difficult to compare quantitatively the degree of neurotoxicity of individual lots and to decide whether this phenomenon was an intrinsic property of streptomycin, one of its "standard" impurities, or a combination of both. My associate Kuna and myself therefore tried to produce neurotoxic signs by intracisternal injection, following the procedure employed by Walker and his associates[4] in their investigation of the neurotoxic properties of penicillin. We found that as little as 1000 units of streptomycin per kg., injected in this manner, produced within 30 to 60 minutes essentially the same effects as the daily intramuscular injection of the same lots in doses of between 100,000 to 300,000 units over a period of at least 10 days (Table I).

Using the technique of electrical recording of ocular movements, my associate Hawkins[5] found, in rabbits receiving streptomycin for a period of 7 to 14 days, that the first sign of chronic, vestibular involvement is a change in the nystagmus in reference to rotation. This change appears 2 to 3 days before disturbances in the animal's gait and posture are obvious. The rate of the rhythmical ocular movements during and after rotation is decreased; ultimately rotation may fail to elicit more than an occasional deviation of the eye.

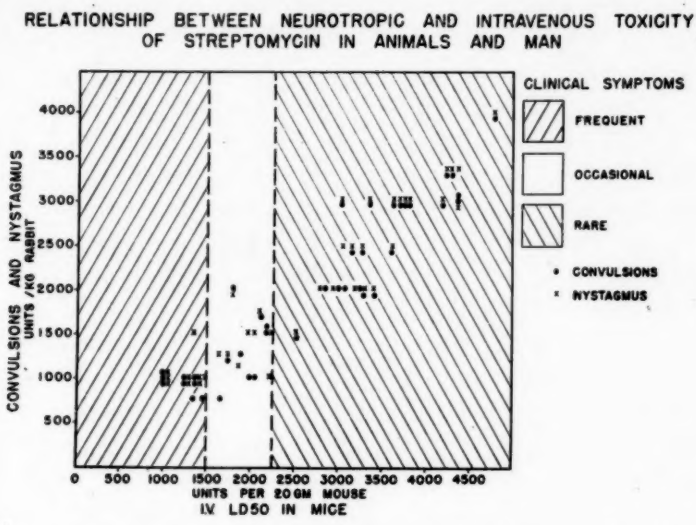

Figure 2. Relationship between neurotropic and intravenous toxicity of streptomycin in animals and man.

Utilizing the technique of intracisternal injection, we compared a large number of streptomycin samples, including many of an early date of manufacture, and determined the number of units necessary to produce in 50 per cent of the animals spontaneous nystagmus. We found not only more than five-fold differences among different batches of streptomycin, but noted also an apparent parallelism between the neurotropic (intracisternal) and general (intravenous) toxicity in animals and the tolerance of the same lots in man (Fig. 2); the latter, however, could not be ascertained for all samples, and the parallelism between neurotoxicity in experimental animals and in man is therefore only suggestive. However, even if we disregard such a possible relationship between the acute toxicity in animals and the tolerance in man, the fact nevertheless remains that wide differences exist among the neurotoxicity of individual lots and that the unit potency of an individual lot is not directly related to its neurotoxicity. These findings strongly suggest that the neurotoxic effects of streptomycin are due, at least in part, to an impurity. Whether the factor responsible for acute death by respiratory failure and determined by intravenous injection in mice is identical with that causing specific neurotoxic non-fatal effects, remains at this

time an open question.

Thus at least two of the serious clinical side-effects of streptomycin may largely, if not solely, be caused by impurities. There are, however, other occasional clinical reactions, such as skin rashes, temporary elevation of body temperature, pain in the joints, and discomfort at the site of injection which cannot yet be reproduced in animals and make it therefore difficult to decide whether they are caused by impurities or are allergic manifestations; the fact that they fail to occur regularly makes it rather unlikely that they constitute intrinsic properties of the drug. At least one of these effects, viz. discomfort at the site of injection, seems to be largely due to impurities since it is far less pronounced with material of greater purity.

The pharmacodynamic effects of streptomycin just described were obtained with samples of varying purity, some as low as 10 per cent, others at least as high as 97 per cent, when evaluated by standard methods. It is quite possible that the small fraction unaccounted for in the latter may be pharmacodynamically inert; however, until a 100 per cent pure streptomycin is available or the exact nature of the remaining impurities is known, it will be impossible to decide with certainty which of the pharmacodynamic effects observed are intrinsic properties of the drug. Based on our present knowledge, however, it would appear, that absolutely pure streptomycin will in large doses depress the medullary centers; that in animals acute death following intravenous injection of extremely large doses will be caused by respiratory failure; that doses within the therapeutic range will not produce serious systemic toxic effects, except a depression of the vestibular and auditory centers; and that pure streptomycin will be free from untoward local reactions. These predictions are based on extensive pharmacological and clinical studies of the most highly purified materials available at this time, material which already conforms with most of these properties.

As with other chemotherapeutic agents, the mode of administration and the dosage regime are most important for the success of streptomycin treatment. For this reason it may be in order to summarize the data on absorption and excretion obtained in experimental animals.

Streptomycin, which is readily soluble in aqueous media, is rapidly absorbed when injected subcutaneously, intramuscularly and intravenously and produces peak concentrations in the blood within as little as 45 minutes after subcutaneous injection and 30 minutes after intra-

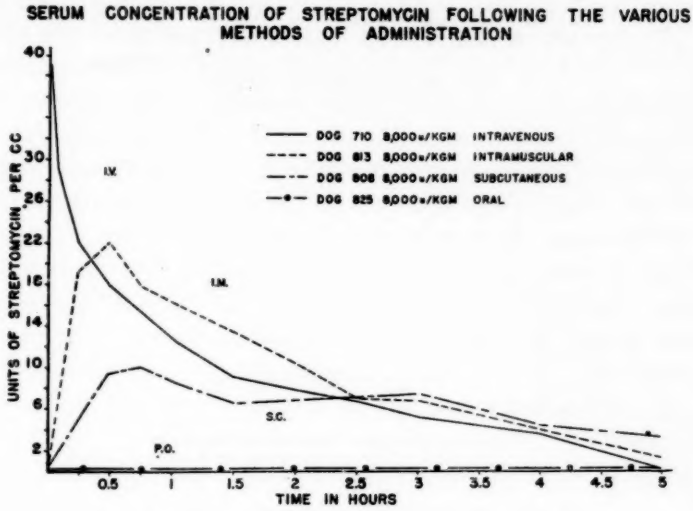

Figure 3. Serum concentration of streptomycin following the various methods of administration.

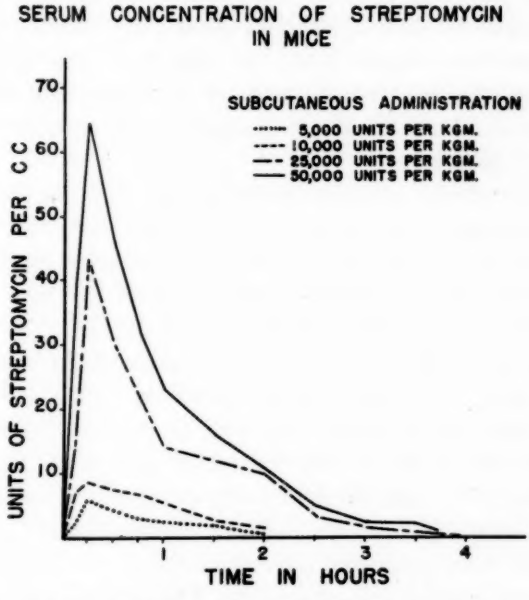
SERUM CONCENTRATION OF STREPTOMYCIN IN MICE
SUBCUTANEOUS ADMINISTRATION
5,000 UNITS PER KGM.
10,000 UNITS PER KGM.
25,000 UNITS PER KGM.
50,000 UNITS PER KGM.
UNITS OF STREPTOMYCIN PER C C
TIME IN HOURS

Figure 4. Serum concentration after streptomycin doses of increasing magnitude.

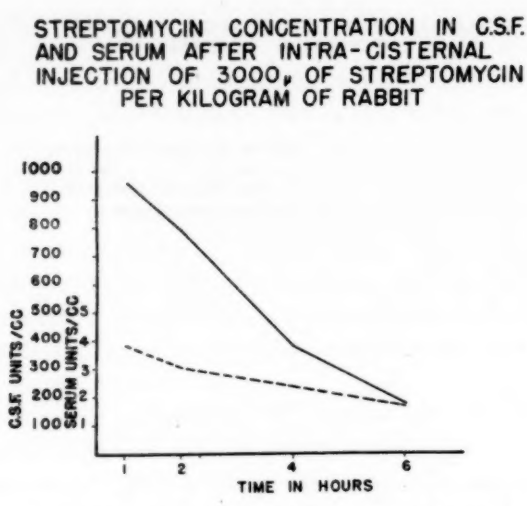

Figure 5. Streptomycin concentrations in cerebrospinal fluid and blood.

muscular injection (Fig. 3). These high concentrations, however, persist only for a relatively short time. As expected, an increase in the dose results not only in a higher peak, but also in a prolongation of the therapeutically effective concentrations in the blood (Fig. 4). For best results repeated administration at frequent, relatively short intervals (3-4 hours) is essential.

The therapeutically effective concentrations vary considerably with the type of organism as well as the individual strain and range from approximately 6 units per cc. for tularemia, which is highly sensitive to streptomycin, to a minimum of approximately 25 units per cc. for less sensitive pathogens such as Salmonella or typhoid.

The amount of streptomycin absorbed after oral administration is too low to affect most organisms; rectal administration, either in form of a microclyster or suppository, produces similar unsatisfactory results. However, the factors influencing the rate of absorption with this mode of administration are not yet sufficiently understood; results are quite erratic, occasionally giving high and well sustained drug concentrations while at other times producing mere traces of the drug in the blood of the same animal without apparent reason. The fact, however, that under certain, not yet controllable conditions, completely adequate absorption

from the rectum may occur, indicates that further investigation of the factors governing absorption from the intestinal tract eventually may render this mode of administration reliable.

Intrathecal and intracisternal injection of streptomycin results in a high concentration in the spinal fluid, but only limited diffusion into the general circulation (Fig. 5). Since the reverse is equally true and the streptomycin concentrations in the cerebrospinal fluid after intravenous injection are rather low, it seems justified to combine intrathecal and intravenous administration whenever a high concentration in the cerebrospinal fluid is needed. However, when using this route it should be remembered that in animals acute neurotoxic reactions may be induced by the intracisternal injection of only a fraction of the dose likely to produce them with other modes of injection. Furthermore, for this type of therapy only material of the highest purity should be used since the impurities contained in less purified material are likely to aggravate the neurotoxic reactions.

While the oral administration of streptomycin fails to produce a therapeutically significant concentration in the blood, the very fact that the drug is not absorbed from the gastrointestinal tract may prove useful in cases where control of the bacterial flora in the intestinal tract is desired. Experiments performed on animals have shown that peroral administration of streptomycin results in a marked reduction in the total count of intestinal bacteria. It would therefore seem justified to make use of the powerful antibacterial action of streptomycin in the preparation of patients for abdominal surgery, using relatively small doses by mouth for 24 to 48 hours before operation and continuing for an equal period postoperatively.

The development of streptomycin resistant strains is undoubtedly one of the most serious obstacles in the prolonged use of this antibiotic. Drug-fastness may develop within a few days and may result in a several thousand fold decrease of the sensitivity of the bacteria to the drug.[6] Experiments in our laboratory by Graessle[7] have indicated that, in line with the earlier work of Carpenter,[8] a combination of the antibiotics streptomycin and penicillin may appreciably retard the development of drug-fastness. However, the most promising way of avoiding this complication is, at this time, the administration of initial doses sufficiently large to effect immediate and complete elimination of the pathogenic microörganisms. In view of the wide variations of bacterial

strains in sensitivity to streptomycin it is therefore highly desirable to determine, first, the relative susceptibility of a given strain and then adjust the streptomycin dose accordingly; it goes without saying, that a mode of administration and a dosage regime must be selected, which will insure the maintenance of an optimal drug concentration at the desired site of action.

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THERAPY OF ERYTHROBLASTOSIS FETALIS WITH EXCHANGE TRANSFUSION*

A. S. WIENER, I. B. WEXLER, *and* T. H. GRUNDFAST

THE first exchange transfusions on infants were performed more than twenty years ago. In fact, in our search of the literature we were surprised to discover a report of a case in which the therapy had been used with success in 1925 for treating an infant with icterus gravis. In this case, reported by Hart,[1] the infant was the result of the eighth pregnancy, had a birth weight of eight pounds and was not jaundiced at first. The seven preceding children had all been born alive, but six of these died following the development of jaundice. On the fourth day of life, jaundice developed in the infant in question, and an exchange transfusion was decided upon in order to "remove enough toxins from the blood to prevent progress of the disease." According to Hart, the method had been brought out and perfected by the late Bruce Robertson while J. L. McDonald performed the actual procedure; 300 cc. of blood were withdrawn from the longitudinal sinus and 335 cc. of donor's blood were injected into the saphenous vein together with 60 cc. of 5 per cent glucose solution. The next day the jaundice was less intense and by the fourth day completely gone and the infant's general condition appeared very much improved. Jaundice reappeared when the child was three weeks old but disappeared spontaneously four days later.

Despite the spectacular success of this first case there is no indication that the procedure was taken up by other workers or even again by Hart himself. Perhaps the operation proved technically more difficult or more hazardous than is suggested by the description in the original article. In addition, lack of knowledge of the role of the Rh factor in the pathogenesis of the disease probably resulted in unfavorable results in subsequent cases.

Our own experiments with exchange transfusions in infants were started in 1944 when we used a technique similar to that described by

* From the Transfusion Division and the Departments of Pediatrics and of Gynecology of the Jewish Hospital of Brooklyn.

Hart, though we were not aware of the existence of his paper at that time.[2] In an experiment performed on an infant with mongolian idiocy, we succeeded in effecting a 90 per cent substitution by withdrawing and injecting 275 cc. of blood. The infusion offered no obstacles but coagulation interfered with the withdrawal of blood, although we tapped in succession the femoral veins, the longitudinal sinus, and a radial artery. When we subsequently applied the method to an infant with icterus gravis, coagulation of the baby's blood caused us to terminate the procedure when only 50 cc. had been withdrawn and 120 cc. injected. The condition of the infant, furthermore, was so good at birth that the treatment seemed to us to be more dangerous than the disease. As happens much too often in such cases the infant subsequently died with kernicterus, and in retrospect there is reason to believe that it could have been saved by a more thorough exchange transfusion.

We planned to carry the work further and considered the use of heparin* as an anticoagulant to facilitate the withdrawal of blood. In 1946, Wallerstein[4] took up the procedure again and performed exchange transfusions in infants, using the technique of Hart. At this time Dr. Peter Vogel[5] informed us that he had succeeded in performing an exchange transfusion by first heparinizing an erythroblastotic infant, and we resumed our experiments. By regulating the dose of heparin, using the saphenous vein for the infusion and the radial artery for bleeding we were able to effect a 90 per cent exchange in an infant with mongolian idiocy by infusing 500 cc. of blood and withdrawing 400 cc. simultaneously.[6] This procedure went much more smoothly and rapidly than did our original experiments and convinced us of its safety. Among other things the relatively enormous amount of citrate injected caused the infant no obvious embarrassment.

It is evident that it is never possible to effectuate a complete substitution of the patient's blood by the donor's because the infusion and bleeding must be done concurrently. As we have shown,[6] if an amount of Rh-negative blood equal to twice the volume of the infant's blood is injected and withdrawal of an equal amount simultaneously carried out, a substitution of approximately 90 per cent will result.**

* Purified heparin had been used successfully by Thalhimer et al.[3] in experimental exchange transfusions in dogs.

** In a newborn infant with an approximate blood volume of 250 cc., about 500 cc. of blood should be injected and simultaneously withdrawn. The magnitude of such an operation can be appreciated when it is pointed out that a comparable procedure in an adult would entail the transfusion of about 10,000 cc. of blood; so that as many as twenty blood donors would be required. Our main experience with large exchange transfusions in adults has been in cases of hemorrhage in which enormous quantities of blood were lost and had to be replaced by transfusion. In one patient, a man with a bleeding duodenal ulcer, as much as 5500 cc. of blood had to be injected before the bleeding was controlled by operation.[7] In a second, more recent case, a woman with an abdominal pregnancy, 7000 cc. had to be transfused before the bleeding was finally controlled. Both patients recovered uneventfully.

The success or failure of this procedure will now depend upon the fate of the remaining 10 per cent of the infant's own Rh-positive red cells. If this residium is eliminated by lysis, no harm will result. But should the cells clump and block the circulation no beneficial effect will have been obtained. While in our earlier cases whole citrated blood was used, an unfavorable experience in one case, which we ascribe to intravascular conglutination of the residual 10 per cent of the infant's Rh-positive blood, has caused us to modify the procedure in subsequent cases by removing one-half of the donor's plasma and replacing this with saline in order to reduce the conglutinin content. Furthermore, whereas in our earlier cases our practice was to inject 100 cc. more than was withdrawn, we have subsequently narrowed this margin to less than 50 cc., in order to avoid the danger of producing a polycythemia. When the blood count is high the viscosity of the blood is increased and the circulation slowed, producing conditions favorable to intravascular clumping.

Obviously, while an exchange transfusion will as a rule arrest the course of the disease, it cannot correct tissue damage that has occurred before treatment is instituted. For this reason it is important to treat the infants as soon after birth as possible. Routine antenatal Rh tests are of great value in indicating ahead of time which infants may require exchange transfusion.

A preliminary report of our experience with our first two cases treated by exchange transfusion has already appeared.[8] Subsequently, we accumulated considerable hematological and clinical data concerning these two patients and we now propose to present a full report. In one case the maternal serum contained univalent Rh antibodies (glutinins); in the other, bivalent Rh antibodies (agglutinins) were present in high titer. Our report will therefore illustrate the contrasting effects of the two varieties of antibodies, and will also act as a standard of reference for subsequent papers in which our experiences with other cases will be described.

CASE 1. Mrs. M. L., 32 years of age, came under the care of one of us (T.H.G.) in February, 1946. She had had one previous pregnancy in 1943 which was complicated at term by placenta previa. She was delivered by Cesarean section of a normal female infant, weighing 6 lbs., 10 oz., who is alive and well. At the time of this operation, the mother was given a transfusion of 500 cc. of whole blood and made an uneventful recovery. She returned during her second pregnancy, and routine Rh tests showed her to be Rh negative and sensitized to the Rh factor, while her husband was Rh positive.

(*Case 1 continued on page* 210)

In view of these findings, a complete study was carried out on the entire family with the results shown in Table I.

TABLE I

RESULTS OF GROUPING AND Rh-Hr TESTS IN CASE 1

Blood of:	*Group and Subgroup*	*M-N Type**	*Rh-Hr Type*
Father	A_1	M	Rh_1Rh_2
Mother	A_1	MN	rh
Daughter	A_1	MN	Rh_1rh

* The M-N types are not important clinically, but are given for the sake of completeness.

Tests for Rh antibodies on the mother's serum gave the following results:

Agglutination Test—Negative

Conglutination Test—Positive (12 units)

These findings indicated that the patient was sensitized to the Rh factor, with antibodies of the univalent variety—the type of antibody which in high titer usually gives rise to hydrops, and in low titer to viable infants with hemolytic anemia.[9, 10] Since the husband belongs to type Rh_1Rh_2, he was almost surely homozygous for the Rh_0 factor, so that every child of this couple would normally be expected to be Rh positive (either type Rh_1 like the daughter, or type Rh_2). Thus, we could be reasonably certain that the fetus which the patient was carrying was erythroblastotic. Since the titer of the maternal antibodies was moderate, there was a good chance of obtaining a viable infant.

The patient having had a previous Cesarean section, this constituted an indication for an elective repeat Cesarean section. This made it possible to select a definite date for the delivery, and two weeks before term seemed to be a favorable time from the standpoint of both mother and fetus.

On the morning of the day chosen for the section, 500 cc. of group A, type rh blood* were drawn from a professional donor and mixed with 60 cc. of citrate solution. The mother was delivered at the Jewish Hospital on September 14, 1946 by a low-flap Cesarean section under fractional spinal anesthesia. It was noted that the amniotic fluid was yellow and the umbilical cord bile stained. The patient was a male with a birth weight of 6 lbs., 9 oz., who appeared slightly pale but had a lusty cry. His liver and spleen were not palpable.

The exchange transfusion on the infant was started immediately.** An incision was made at the ankle, a blunt 20 gauge cannula inserted into the saphenous vein, and the infusion of blood started. The radial artery on the opposite side was exposed at the wrist. Then, 0.2 cc. (200 units) of heparin† was injected into the saphenous vein. The radial artery was nicked and the infant's blood allowed to flow freely through the opening. By this time, approximately 75 cc. of the donor's blood had run into the saphenous vein.

(*Case I continued on page 212*)

* Since both parents belonged to group A, the expected infant had to be either group A or group O. If the infant proved to be group A, it would be unwise to completely replace its blood with group O blood because the anti-A agglutinin in such a large quantity of donor's blood might harm the infant; obviously such an infant would have to receive A blood. Group A blood would also be acceptable even if the infant belonged to group O. The reason for this is that whatever antibodies an infant has at birth are derived from the mother, so that the expected infant in our case could not have any alpha antibodies.

** Though blood specimens were taken for laboratory examinations, the procedure was not delayed pending the reports.

† This was provided through the courtesy of the Upjohn Company.

TABLE II

RESULTS OF HEMATOLOGIC STUDIES IN CASE 1

	Time when test was made														
	At birth	*4 hrs.*	*2nd day*	*3rd day*	*4th day*	*5th day*	*6th day*	*7th day*	*10th day*	*14th day*	*25th day*	*34th day*	*40th day*	*59th day*	*82nd day*
Hemoglobin per cent	81	117	112	112	122	122	112	105	98	98	80	56	65	70	67
RBC (mill./c.mm.)	—	5.36	5.82	5.65	6.34	5.93	5.76	5.37	4.78	—	3.46	2.9	3.05	3.14	3.44
WBC (mill./c.mm.)	—	12,200	20,000	21,800	7,900	7,900	10,400	9,900	14,100	—	14,200	8,500	10,700	12,100	11,500
Neutrophiles															
segmented	54	59	71	77	23	24	19	23	38	41	27	25	27	19	30
band	6	22	18	7	17	5	8	6	13	4	7	3	2	2	4
young	1	6	5	2	0	0	1	0	1	0	0	0	0	0	0
myelocytes	2	1	1	4	1	0	6	5	4	0	0	0	0	0	0
Eosinophiles	1	0	1	3	20	23	10	9	7	1	12	2	2	2	5
Basophiles	0	0	0	0	0	0	3	0	0	0	0	1	0	0	0
Lymphocytes	28	8	3	6	17	39	44	48	29	45	47	62	60	69	52
Monocytes	8	4	1	1	22	9	9	9	8	9	7	7	9	7	9
Nucl. RBC/100 wbc.	69	20	19	5	2	none	none	none	none	none	none	none	none	1	0
Reticulocytes	—	1%	3%	—	1%	1%	0.5%	—	rare	none	none	rare	3%	2%	—
Icterus Index	35	—	—	50	—	50	—	40	35	—	—	—	—	—	—
Anisocytosis	marked	occ.	occ.	none	none	none	none	none	none	none	none	none	none	none	none
Polychomasia	frequent	frequent	frequent	none	rare	none	none	none	none	none	none	none	none	none	none
Stippling	none	rare	none	occ.	rare	none	none	none	none	none	none	none	none	none	none
Differential agglutination	100% Rh_1	$^1/_{10}Rh_1+$ $^9/_{10}rh$	$^1/_{10}Rh_1+$ $^9/_{10}rh$	—	—	—	—	100% rh	100% rh	100% rh	100% rh	100% rh	$^1/_8Rh_1+$ $^6/_8rh$	$^1/_2Rh_1+$ $^1/_2rh$	$^9/_{10}Rh_1+$ $^1/_{10}rh$

During the entire procedure it was attempted to keep the infusion approximately 50 to 75 cc. ahead of the bleeding in order to allow a margin of safety. The heparin injection was repeated two more times—the last (third) injection being given at approximately the middle of the procedure, with the idea that the heparin effect would then be nullified by the time the transfusion was completed. The bleeding was so free that it was necessary to apply pressure intermittently to the radial artery in order to permit the infusion to keep pace with it.* After a total of 430 cc. of blood had been obtained, the radial artery was doubly ligated and the skin sutured. The infusion was continued until the entire 560 cc. of citrated blood had run in. At the end of the procedure, it was noted that the infant appeared bloated and lethargic, and its precordial impulse seemed rapid and weak. That these symptoms were due to overloading of the circulation was supported by the observation that the spleen had become markedly enlarged. Apparently some miscalculation had occurred, because we now found the infant's weight to be 7 pounds, that is, 7 oz. above birth weight. The infant responded well to stimuli, and since the plethora did not appear to cause him excessive embarrassment, he was sent to the nursery.

The infant's course in the hospital was observed closely clinically and by daily hematological examinations, the results of which are given in Table II. The blood smear taken immediately after birth showed marked abnormalities of the erythrocytes, with anisocytosis, frequently polychromatic macrocytes, and 69 nucleated R.B.C. per 100 W.B.C. In the grouping tests on the infant's blood before transfusion, reactions corresponding to group A, type M, type rh′ were obtained. However, when two drops of the baby's blood suspension were placed in a test tube, centrifuged, the supernatant fluid removed and replaced by a drop of compatible oxalated adult plasma, clumping (conglutination) occurred upon further incubation in the water bath. This proved that the infant's erythrocytes were coated with univalent Rh_0 antibodies and that it really belonged to type Rh_1 and not to type rh′.**

Four hours after the exchange transfusion, a blood count showed that the hemoglobin concentration had risen to 117 per cent with an R.B.C. count of 5.36 million per c.mm. At this time the infant appeared quite well and active, and the spleen seemed slightly smaller. The subsequent course in the hospital was essentially uneventful. There was a gradual decline in the R.B.C. count and hemoglobin concentration, but on the 10th day, these were still within normal limits. The nucleated R.B.C. disappeared from the smears by the fifth day, at which time reticulocytes also became scanty. The cord serum had an icterus index of 35 units, but jaundice was not noticeable clinically until the second day and then only on the face. It was most noticeable between the fourth and sixth days and then gradually receded, at no time being at all pronounced. Differential agglutination tests on the infant's blood immediately following the transfusion showed that a replacement of approximately 90 per cent had been accomplished. The infant's own remaining cells soon disappeared so that after the seventh day, its blood reacted as A,MN rh, that is, the type of the donor.

As a matter of interest, the maternal Rh antibodies were titrated following the delivery in order to determine whether a Cesarean delivery stimulates an antibody rise like a normal delivery. A three-fold increase in titer was observed, indicating that during Cesarean delivery, a shower of fetal cells probably enters the maternal circulation, just as in birth per vaginam. Thus, Cesarean delivery does not protect the mother from becoming sensitized.

The infant's subsequent course was uneventful. There was the usual period of apparent aplasia, so that the blood count gradually declined as the donor's erythrocytes

(*Case I continued on page 213*)

* In subsequent cases we permitted the bleeding to continue unchecked and speeded up the infusion with the aid of syringe and 3-way stop-cock. In this way the procedure could be completed in a shorter time (60—90 minutes).

** Similar observations on erythroblastotic infants have been reported by one of us (W.) previously [11, 12]

disappeared from the circulation. At the age of one month, the hemoglobin concentration was still 80 per cent. Reticulocytes appeared on the blood smear at the end of the fifth week, at which time the hemoglobin concentration was only 56 per cent. If one assumes that the amount of blood administered was sufficient to give the infant a hemoglobin concentration of 100 per cent and that the survival period of the transfused erythrocytes in newborn infants is 12 weeks, then in a five week period during which there is no regeneration, we would expect the blood hemoglobin concentration to drop to seven-twelfths of 100 per cent or to about 58 per cent. The observed hemoglobin concentration of 56 per cent is very close to that expected under this hypothesis.*

Following the appearance of reticulocytes in the blood smear, the blood regeneration not only kept pace with, but even exceeded, the rate of destruction of the donor's red cells so that by the sixth week the hemoglobin concentration was 65 per cent. At that time the differential agglutination tests clearly revealed the presence of the infant's own Rh-positive red cells. By the end of the third month all the cells in the circulation were Rh positive. Throughout the course, the infant appeared and behaved perfectly normal except for the jaundice during the first two weeks of life.

The advantage of the exchange transfusion in this case was that it did away with the need for repeated transfusions and it spared the infant's body the task of getting rid of the products of hemolysis. Of course, its most important purpose was to preclude the possibility of intravascular conglutination.

In Figure 1 we have summarized the most important hematologic findings of Case 1. The resemblance between this figure and one previously published[2] in connection with a case of erythroblastosis fetalis (hemolytic anemia variety) treated by simple transfusions with Rh-negative blood is striking. The reason for this is that in that earlier case we accomplished what really amounted to a complete exchange transfusion. The circumstances in that case were very similar, the mother having had a previous erythroblastotic infant delivered by Cesarean section and the husband being homozygous Rh positive (type Rh_1Rh_2). Five hundred cc. of blood were drawn from group O, type rh professional donor in preparation for an exchange transfusion, but when the infant was delivered by Cesarean section, she proved to be already practically exsanguinated, due to a severe hemolytic anemia. An immediate transfusion of 160 cc. of the blood revived the infant and subsequently 75 cc. more were administered. In this way, a complete exchange transfusion was accomplished, though we were spared the task of bleeding the infant.

As Figure 1 demonstrates, the curve of elimination of donor's erythrocytes from the infant's body is practically linear. The reason for

* Since infants grow rapidly during the neonatal period, their blood volumes also increase relatively rapidly. In the presence of bone-marrow aplasia, this factor alone could cause a gradual decline in the blood count. This may also account for our observation that transfused red cells appear to survive only three months in infants, in comparison with a maximum survival period of four months for adult recipients.

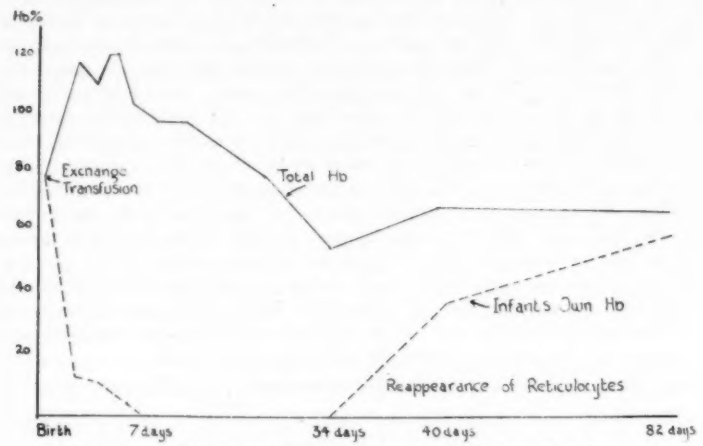

Figure 1. Results of Differential Agglutination Tests in Case 1

this, as was first pointed by one of us,[13, 14] is that the blood obtained from the donor is actually a mixture of red cells of all ages. Naturally, the older cells wear out earlier and disappear first from the recipient's circulation and, as has already been pointed out, the infant's hemoglobin concentration can be predicted arithmetically by postulating a maximum survival period for the donor's erythrocytes of twelve weeks. As the infant's total red cell count drops, the question will arise whether the infant should be re-transfused. In making this decision, one should be guided not only by the blood count, but also by the smear for reticulocytes and the differential agglutination tests. The appearance on the smear of a shower of reticulocytes is a sign of active regeneration—and in such cases, transfusions may be withheld even when the hemoglobin concentration is as low as 50 per cent. If the differential agglutination tests show no Rh-positive cells and there are no reticulocytes on the smear, a small supplementary transfusion of about 60 to 70 cc. of blood may be advisable when the hemoglobin concentration drops below 60 per cent.

An interesting observation is the presence of a high eosinophilia which persisted up to the sixth week of life. The coincidence between the period of the eosinophilia and the period of bone marrow aplasia supports the idea[2] that the apparent aplasia is due to the persistence in the fetal body of maternal Rh antibodies which destroy any new ery-

TABLE III

Blood of	*Group*	*M-N Type*	*Rh-Hr Type*
Father	O	MN	Rh_1rh
Mother	O	M	rh
Older Brother	O	M	Rh_1rh
Patient	O	MN	Rh_1rh

throcytes as quickly as they are released from the bone marrow. That is, the eosinophilia probably reflects the continued presence of an antigen-antibody reaction in the infant's body.*

CASE 2. The patient was a female infant born at the Adelphi Hospital on September 24, 1946. Shortly after birth jaundice was noted, and the possibility of erythroblastosis was considered despite the fact that the blood count was normal. The infant was the second child. The results of grouping and Rh-Hr tests on the family are shown in Table III. Tests for Rh antibodies in the mother's serum revealed the presence of anti-Rh_0 agglutinins of 50 units titer.

Since the presence of anti-Rh agglutinins (bivalent antibodies) of such high titer is usually associated with the syndrome of icterus gravis the patient was in imminent danger of developing kernicterus. An immediate exchange transfusion was carried out; 500 cc. of group O, type rh blood were injected and 450 cc. withdrawn. The procedure went very smoothly. Approximately 100 cc. of blood had run into the infant by the time the bleeding had started, and this initial advantage was maintained throughout the procedure. The total dosage of heparin was again 0.6 cc., administered in divided doses of 0.2 cc. each, the last being given at about the middle of the procedure. The heparin effect had been completely nullified by the time the procedure was completed so that it was not even necessary to ligate the blood vessels.

The infant's subsequent course was uneventful. Jaundice disappeared within twenty-four hours and thereafter the baby exhibited no further evidence of the disease.

The hematological findings before and after the transfusion are shown in Table IV. It will be seen that before transfusion the blood count was essentially normal and the smear showed only 2 nucleated red blood cells per 100 W.B.C. However, there were many polychromatic erythrocytes present and the icterus index was 45 units. On the day following the transfusion (fourth day of life) the hemoglobin concentration of the blood was 113 per cent and the blood smear showed no abnormalities, there being no polychromatic cells or nucleated red blood cells. Differential agglutination showed that a 90 per cent replacement had been effected. On the sixth day the hemoglobin concentration was found to be 95 per cent and differential agglutination showed that this drop

(*Case II continued on page 217*)

* The relatively continuous presence of an eosinophilia in cases of erythroblastosis while there is an antigen-antibody reaction going on has suggested to one of us (W.) a new line of investigation. As is well known, histamine is released during allergic reactions but the source of the histamine has never been satisfactorily explained. The idea that histamine may be derived from the eosinophilic granules deserves consideration for the following reasons: (1) There is a close correlation between the release of histamine and eosinophilia. (2) The histamine concentration of the blood is highest in the white blood cell layer. (3) The acidophilic staining reaction of the eosinophile granules could readily be explained by the presence of a base like histamine. Direct evidence supporting this theory has already been reported by Code.[17]

TABLE IV

RESULTS OF HEMATOLOGIC STUDIES IN CASE 2

	Time when tests were made									
	3rd day; before exchange transfusion	*4th day*	*6th day*	*10th day*	*15th day*	*22nd day*	*43rd day*	*57th day*	*74th day*	*90th day*
Hemoglobin per cent	117	113	95	90	90	90	70	75	75	72
RBC (mill./.mm.)	5.5	—	4 3	4.3	4.7	4.3	3.51	3.69	—	—
WBC (mill/c mm.)	16,000	—	11,400	9,800	15,600	12,800	—	—	—	—
Neutrophiles: segmented	40	44	49	45	45	31	18	28	18	—
band	4	5	5	2	3	2	1	1	1	—
Lymphocytes	45	39	30	46	42	56	70	58	74	—
Monocytes	7	8	13	3	8	7	7	6	3	—
Eosinophiles	2	3	3	3	3	3	4	7	4	—
Basophiles	1	0	0	1	0	1	0	0	0	—
Myelocytes	1	1	0	0	0	0	0	0	0	—
Nucl. RBC/100 WBC	2	none	none	none	none	none	0	0	0	—
Reticulocytes	3%	none	none	none	1/2 %	1/2 %	1/2 %	1/2 %	1%	1/2 %
Differential agglutination	100% Rh_1	$^1/_{10}Rh_1 + ^9/_{10}rh$	100% rh	100% rh	100% rh	$^1/_{20}Rh_1 + ^{19}/_{20}rh$	$^1/_2Rh_1 + ^1/_2rh$	$^{11}/_{15}Rh_1 + ^4/_{15}rh$	—	99% Rh_1

was due to the elimination (by hemolysis) of the remainder of the infant's own Rh-positive red cells. How severe the disease process might have been if the infant's blood had not been withdrawn can, of course, only be surmised. The complete and rapid destruction of the residual 10 per cent indicates that the process would almost surely have been severe. On the 15th day the hemoglobin concentration was still 90 per cent, and by this time reticulocytes reappeared on the blood smears, so that effective regeneration had already begun. From this time onward the blood count was maintained within safe limits as the production of the infant's own cells practically kept pace with the elimination of the donor's erythrocytes. The infant's red cells were once more demonstrable in the differential agglutination preparations as early as the twenty-second day of life.

The less impressive hematological findings in this case as compared with case 1 may be explained by the difference in the type of antibody produced by the mother. According to the evidence presented by Wiener,[9, 15] univalent antibodies, such as were found in case 1, pass the placental barrier more readily than do the bivalent antibodies such as were found in this case. In typical cases, the univalent antibodies coat the fetal red cells and give rise to a gradually progressive hemolytic anemia. These antibodies are capable of traversing the placenta only during the last trimester of pregnancy, at which time, if they are of sufficiently high titer, they may give rise to stillbirths. If the child is born alive and has good hepatic function, jaundice will be minimal. If hepatic function is poor, jaundice and its accompanying toxicity will be present, laying the ground work for kernicterus to develop, should intravascular conglutination with capillary damage to the brain occur. Bivalent antibodies, on the other hand, apparently gain access to the circulation principally during parturition, and the infant at delivery often appears quite normal. When intravascular agglutination takes place, it usually occurs without warning so that an infant who appears to be thriving may die suddenly without developing anemia. We were fortunate in case 2 to be able to institute treatment before intravascular agglutination occurred. Not every case in which the maternal serum contains bivalent Rh antibodies is doomed to have kernicterus. The clumping of the red cells is a reversible process up to a certain point in vivo as well as in vitro, so that the flow of circulation tends to cause dispersion of the cells as quickly as the clumps form. This process of repeated agglutination and dispersion of the red cells damages them so that in such cases a rather abrupt drop in the hemoglobin is not an unusual finding. This mechanism may explain the sudden drop in hemoglobin that occurred in case 2. Differential agglutination proved the drop to be due to the elimination of the infant's own Rh-positive cells

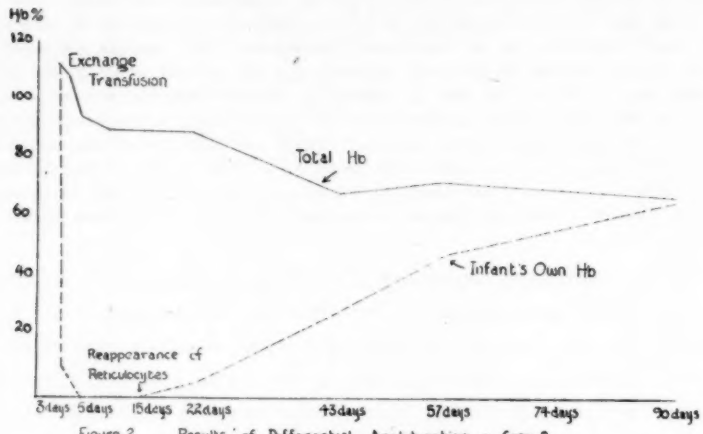

Figure 2 Results of Differential Agglutination in Case 2

rather than the donor's cells because thereafter all of the circulating erythrocytes were type rh.

Of interest is the relatively short period of apparent bone marrow aplasia* in this case as contrasted to that of case 1 (cf. Fig. 2). This is understandable on the hypothesis that the agglutinins enter the body of the infant mainly during labor and were largely removed by the exchange transfusion. On the other hand, univalent antibodies pass through the placenta continuously during the latter part of pregnancy and accumulate in the fetal body in quantities large enough not only to coat the erythrocytes, but also to permeate the blood serum and tissue fluids. Therefore, in such cases only a small portion of the antibodies are removed by the exchange transfusion.

Discussion

While this paper was in preparation a communication by Wallerstein[16] appeared, in which he described the results of twelve cases treated by substitution transfusion. In ten of these cases the blood was withdrawn from the sagittal sinus, while the radial artery was used in only two cases. Nine of the twelve cases treated recovered. Of the three cases that died, one had been given heparin to facilitate the bleeding from the radial artery and at autopsy a tentorial laceration with marked

* Since the apparent aplasia is really due to hemolysis of the infant's red cells by the Rh antibodies remaining in its body, as quickly as the cells are released from the bone marrow, this period is perhaps better named "the phase of ineffectual regeneration."

hemorrhage was found. Wallerstein concludes that since silent intracranial hemorrhage is relatively common in the newborn infant, heparin is a dangerous drug to use.

As a matter of fact, our experience has proved that heparin administered according to our dosage schedule is perfectly innocuous. To date, we ourselves have treated nine infants, and three additional infants were treated by three other workers following our directions. All but one of these twelve infants made a spectacular recovery, although five of them were desperately ill when treatment was instituted. The infant who died showed, at post-mortem, kernicterus with liver damage, but no evidence of any hemorrhage. Incidentally, this patient was given 100 cc. more blood than was withdrawn. Had our modified technique been used, in which one half the donor's plasma is removed and replaced with saline and the amount of blood injected is not allowed to exceed by more than 50 cc. the qauntity of blood withdrawn, we believe that the outcome even in this case would have been favorable. In addition, P. Vogel informs us that he has performed five exchange transfusions with the aid of heparin, all with favorable results. It therefore seems obvious to us that in the case Wallerstein mentions the death was due not to the heparin but rather to the hemorrhage secondary to the tentorial tear. After all, infants who have not received heparin frequently die as a result of intracranial hemorrhage caused by tentorial tears.

Summary

Two cases of eythroblastosis are described in detail, which were treated by the method of exchange transfusion. In one case, the maternal serum contained univalent Rh antibodies (glutinins) and the other case bivalent Rh antibodies (agglutinins). These cases illustrate the spectacular effect of exchange transfusion in treating erythroblastosis. By the method of differential agglutination it was demonstrated that in the infant whose mother had the univalent antibodies the infant had a period of apparent aplasia persisting up to the thirty fourth day, while in the infant whose mother had bivalent antibodies the period of aplasia terminated on the fifteenth day. This supplies further evidence to support the thesis that the different clinical manifestations of erythroblastosis are due to differences in the quality of the maternal Rh antibodies.

The method of exchange transfusion described is simple. It entails

the use of heparin, the injection of the donor's blood into the saphenous vein at the ankle, and the withdrawal of the infant's blood through the radial artery at the wrist. Of a total of seventeen infants treated by this technique, many of whom were critically ill, all but one made a prompt and lasting recovery. This demonstrates the effectiveness as well as the safety of the procedure.

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EIGHTY YEARS OF PUBLIC HEALTH IN NEW YORK CITY*

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SIR Ronald Ross once wrote that most people take the great medical discoveries for granted because they have no conception of the vast number of workers and the years of effort that were necessary to make those discoveries possible. The present advanced state of public health is not due to any one person. It exists today because many men and women dreamed and planned and labored. They worked ceaselessly until their theories were translated into actualities.

This year marks the eightieth anniversary of the founding of the Department of Health of the City of New York. However, that doesn't mean that it is only eighty years that the City administration has been interested in the health of the people. Soon after the Revolutionary War, attention was given to the health problems of the day. These consisted, for the most part, of epidemics of yellow fever that reached New York and Boston. In 1798 the inhabitants of this City were panic-stricken by the rapid spread of this dread disease, and they fled as far north as Greenwich Village hoping to outdistance it. At that time New York City had a population of 60,000. Two-thirds of the residents were stricken with yellow fever, and of these 1,500 died. Sixteen of the forty physicians practicing lost their lives in that one epidemic. Up to that time the City had no power to make health regulations, but the need for such power in order to meet emergencies was recognized and in 1799 the State Legislature granted the City authority to pass its own health laws.

The first written evidence of the existence of health administration in New York City is the report made in 1806 by John Pintard who was City Inspector during the first decade of the nineteenth century. The exact date when he took office is uncertain but he was appointed March 26, 1804. The report was addressed to DeWitt Clinton who was

* Address delivered at The New York Academy of Medicine November 8, 1946 before the Section of Historical and Cultural Medicine and the New York Society for Medical History.

Mayor of the City and President of its Board of Health.

Pintard recorded that six hundred persons had died of yellow fever in 1805. In that year the population of New York City was 75,000. This made the death rate from yellow fever 8 per 1,000 of population.

The City Inspectors who served in the early part of the century were keenly aware of the importance of accurate vital statistics. In his report of 1810 Inspector Pintard pointed out that the statistics of the day could not be depended on in every instance because of incomplete and, in some cases, erroneous reporting. He felt that accurate records would make "bills of mortality" of incalculable benefit not only to physicians but to all interested in the health and welfare of the people.

City Inspector Dunnell in 1838 also called attention to the need of reliable statistics. He was the first inspector to recommend the maintenance of a registry of births and marriages. Cornelius B. Archer, City Inspector in 1845 and 1846, succeeded in securing the enactment of a law providing such registration. It was not very effective because there was no penalty for failure to report. Archer also urged improved sewerage, and the establishment of a hospital for pestilential and epidemic diseases. His successor was A. W. White who labored unceasingly to have the City's vital statistics accurate. White was also very much interested in the nomenclature of disease. He recommended that a complete sanitary survey be kept in the office of the City Inspector. He was the first inspector to make such a survey. In his report of 1850 he called attention to the salutary effect the introduction of Croton water six years earlier had had on the health of the people.

Apparently convinced of the value of the recommendations of his predecessors regarding vital statistics and analyses of sanitary conditions, Thomas K. Downing, City Inspector from 1852 through 1854, established two bureaus, that of Sanitary Inspection and that of Registry and Statistics. These bureaus have remained as part of the organization of the Health Department.

Inspector Morton who served from 1855 through 1857 was interested chiefly in sanitary matters. Incidentally he kept very careful records, and the City's vital statistics of those years are quite dependable. He was a pioneer in recommending greater playground facilities for children and the construction of experimental dwellings. Thus the recognition that proper housing and adequate recreational facilities are intimately related to public health is not as recent as many people think.

Inspector Delevan in 1858 complained of crowded, ill-ventilated railroad cars. Time hasn't brought any radical change in this matter because similar complaints can be heard today.

Dr. Stephen Smith in his book, "The City That Was," referred to the City Inspectors as incompetent and corrupt. Some of them undoubtedly were, but it would be unfair to brand all of them as such. Many, as those mentioned above, were honest, intelligent and capable men working under great handicaps. They succeeded in instituting measures which are recognized today as sound public health practice.

You may wonder why mention is made of a Board of Health long before the establishment of the Metropolitan Board in 1866. Boards of Health were temporary committees called by the State Legislature to deal with specific emergencies such as yellow fever and cholera epidemics. A State law in 1807 empowered the Common Council of the City to appoint a Board of Health consisting of the Mayor, the Recorder, the Commissioners of the State Quarantine Office and five other members. This Board recommended measures to the Common Council for dealing with health emergencies. Very often the measures were much more costly than they were effective. Once when a cholera outbreak threatened, it was suggested to Mayor Fernando Wood that he call a meeting of the Board of Health. He replied that the Board was more to be feared than the pestilence.

It is important that we recall something about the City as we trace its public health development. In the first quarter of the last century the northern boundary of the built-up portion of the City was Canal Street. The City appears to have been reasonably clean and tidy. On the whole, housing was favorable, and gardens and orchards were common. There were no tenements. Water was obtained from private wells. Some purchased it from a company that piped it through wooden conduits laid beneath the streets, while others bought it a bucketful at a time from peddlers driving a horse-drawn cart resembling a modern street sprinkler. There were outdoor privies. Water closets didn't appear until after the introduction of Croton water in 1842. The general death rate was about 25 per 1,000 population, and the infant mortality ranged between 120 and 140 per 1,000 live births. It must be remembered, however, that the statistics weren't entirely accurate at that time. New York City was relatively free of serious epidemics during the first quarter of the nineteenth century, although yellow fever which

had devastated the City in 1798 reappeared in 1805 and 1822.

In the second quarter of the century conditions changed rapidly. The City grew by leaps and bounds. The invention of the steam engine ushered in the industrial revolution. In 1845 a severe famine in Ireland caused thousands to emigrate to this country, and in 1848 the great social revolution which swept through Europe brought additional thousands of immigrants to our doors. The housing situation became acute. Poorly constructed houses were erected and cellars became living quarters. In the struggle for survival workers, especially the unskilled, were forced to work for less and less. The standard of living dropped sharply, and the panic of 1837 accelerated this drop. The City became increasingly insanitary. Three cholera epidemics, one in 1832, another in 1834 and the third in 1849, took nearly 10,000 lives. By 1850 the infant mortality rate had risen to 180 per 1,000 live births.

It was late in this second quarter of the century that the campaign for pure milk began, and surprising as it may seem this was incidental to a temperance crusade. The man who was responsible for calling attention to the need for reform in the milk industry was a prohibitionist named Robert Hartley. He found that the mash which remained after the whiskey had been made was sold to dairymen for feed. He visited barns and stables to see what effect this diet had on the cows. He found both the cows and the places where they were housed in a deplorable condition. The cows were undernourished, many of them diseased, and the places where they were kept were unbelievably filthy. In 1848 the Academy of Medicine which was then only a year old appointed a committee to study the milk situation. Despite its efforts and those of Frank Leslie, the publisher, very little was accomplished. More than sixty years were to pass before the people living in New York City had a safe and wholesome milk supply.

It was during this same second quarter of the nineteenth century that Edwin Chadwick, a lawyer living in England, put forth the thesis that the care of the health of the population was a function of good government. He had been influenced by Jeremy Bentham who, earlier in the century, had said, "All factors which influence the health of a community must be the concern of a legislature." In 1842 Chadwick made his famous "Report on the Sanitary Condition of the Labouring Population of Great Britain," which stimulated much interest. Six years later, a general Board of Health was created in England. Chadwick

was assisted by Southwood Smith, a physician. This partnership of law and medicine in behalf of public health was repeated in New York City a quarter of a century later when Dorman B. Eaton, a lawyer, and Stephen Smith, a physician, drafted the bill creating a Metropolitan Board of Health. In the opinion of as great an authority as the late Dr. William H. Welch, Eaton's contribution to health administration in this country ranks with that of Chadwick in England.

The third quarter of the nineteenth century brought with it a continuance of the rapid growth of the City with an accompanying increase in insanitary conditions. There was great dissatisfaction concerning the filthy condition of the streets and the general inefficiency of the health administration. It was a common practice to throw garbage and papers in the street, and these remained there for long periods of time. Dr. William Guilfoy who for many years was Registrar of Records in the New York City Department of Health was born in 1859 in the lower west side not far from the Washington Market. He told how youngsters in his day would earn a few nickels by standing at Broadway near City Hall with a broom, and when a lady or a gentleman wanted to cross the street, they would sweep a path through the muck.

In the early 60's, there were nearly two hundred slaughter houses in the City, many of them in thickly populated sections. Cattle, hogs and sheep were constantly driven through the streets, which were soon covered with their excreta. Blood and refuse from the slaughter houses added to the filth. Manure heaps from the numerous stables and farms were ever-present.

These facts were included in the report prepared by the Citizens' Committee of which Peter Cooper was president. The object of this Committee was to seek reform in all branches of municipal government. The bill for the establishment of a Health Department and a Board of Health in New York City was first drafted by Dr. Smith, Chairman of the Committee's Council of Hygiene and Public Health, and was put into final form by Mr. Eaton, the Committee's Counsel. It was passed by the Legislature in 1866.

Even prior to this time, namely in 1858, the Senate appointed a "Select Committee" to examine health administration in the city and to recommend legislation necessary to increase its efficiency. Apparently the report of this committee was not strong enough to bring about the needed change in health administration, for nothing was done. It was

for this reason that the Citizens' Committee was formed. Then, as now, intelligent citizens banded together to fight for essential reforms.

As organized under the Act of 1866, New York City's health administration was placed in the hands of a Board of Health for the metropolitan sanitary district of the State of New York. This district comprised the counties of New York, Kings, Westchester and Richmond, and the towns of Newtown, Flushing and Jamaica in the county of Queens. In 1870 the Board's jurisdiction was limited to the old City which included only the Boroughs of Manhattan and the Bronx. The first Board consisted of a president, appointed by the Mayor, four physicians who were sanitary commissioners, the health officer of the Port of New York and four police commissioners. A physician was appointed as sanitary superintendent in charge of the Bureau of Sanitary Inspection, and another physician was made Registrar of Vital Statistics. Mr. Eaton was named counsel. The Board of Health was empowered to make laws governing health and sanitation and to sit in judgment on violators. It is to the credit of the men who drafted the bill establishing the Board of Health that they recognized the need for giving it such broad and unprecedented powers.

During the first year of the Board's existence, there was a severe cholera epidemic in the City. Two army barracks were converted into hospitals and were placed under the supervision of Dr. Stephen Smith. Dr. Smith was also directed to organize a corps of physicians, some of whom would work in the dispensaries and others who would make house-to-house visits. Certain buildings were selected which could be used as temporary quarters for those families that would be removed from houses in which there were cases of cholera. The report of 1866 goes into considerable detail concerning the disinfectants utilized. Those most frequently employed were sulphate of iron, chloride of lime and soda, permanganate of potash, carbolic acid, and sulphur for fumigation.

It must be remembered that when the Health Department was formed, the germ theory of disease was still unknown and the chief function of the Department was the elimination of nuisances and the improvement of sanitation. Epidemics were fought by trying to neutralize the noxious gases in the atmosphere, gases which were the result of putrefying animal and vegetable matter.

It was the sanitary superintendent, Dr. Edward B. Dalton, who or-

ganized an ambulance service for Bellevue Hospital in 1869. Dr. Dalton, a colonel in the Civil War, had had considerable experience with the transportation of wounded soldiers. The removal of cases of smallpox had formerly been under the jurisdiction of the metropolitan police, but was now transferred to the Board of Health. Thus, the first satisfactory hospital ambulance service in New York City originated with the Health Department.

According to its second annual report, the Board of Health was concerned with the great prevalence of venereal diseases in New York City. It recommended that all hospitals and dispensaries receiving financial assistance from the State be obliged to treat venereal diseases.

In 1868 and 1869, important activities of the Department of Health included: Fixing a standard for illuminating oil; installing public drinking fountains in various parts of the city; erecting a public comfort station at Astor Place; taking action against the escape of offensive odors from lime and shellburning establishments; making a city-wide survey of tenement houses; and providing for the destruction of dogs believed to be rabid.

Although not established as a Bureau until many years later, the beginning of the Food and Drug Division was made in 1868 with the appointment of Professor Charles F. Chandler as chemist to the Department. Chandler's analyses showed that a fraud was being perpetrated on the public by the systematic dilution of milk with water. He estimated that the dilution was costing the people of this City about $12,000 a day. In 1869 he turned his attention to the cosmetics that were being sold in the city. This was in response to a resolution of the Board that he examine hair tonics, washes and restoratives to find out if they contained injurious matter. His analyses revealed the presence of considerable quantities of lead. The next year he continued his examination of cosmetics and said, "Periodical publication of poisonous cosmetics would undoubtedly diminish the evil to a great extent."

By 1870, two more bureaus had been added to the Health Department—the Bureau of Street Cleaning and the Bureau of Sanitary Permits. In that year also, 200 cases of yellow fever occurred on Governor's Island, the first appearance of this disease in New York City since 1822. Dr. J. C. Nott, a physician practicing in this city, leaned strongly towards the germ theory of disease in discussing the nature and spread of yellow fever. He even suggested that it might be com-

municated by insects.

In 1871 there were reported in New York City 3,084 cases of smallpox with 805 deaths from that disease. In the same period, there were 146 cases of typhus fever. During that year, 100,000 persons were vaccinated.

The subject of infant mortality wasn't given much consideration until 1874 by which date the City's rate had climbed to approximately 240 per 1,000 live births. Then there was clamor for some action that would halt the steady rise. A leaflet on infant care was printed in simple language and distributed to tenement house dwellers. In the same year the Board of Health was confronted with the smoke nuisance created by the New Haven, Harlem and Hudson River railroads above 42nd Street. The Board condemned this as detrimental to public health and appointed a committee to confer with the superintendents of the railroad who, the report states, were most cooperative and did what they could to reduce the smoke to a minimum.

Smallpox was a serious problem in 1874 and the Legislature transferred the smallpox hospital from the jurisdiction of the Commissioners of Charities and Corrections to the Health Department, changing its name to Riverside Hospital. During the winter of 1874 and 1875, two thousand cases of smallpox were reported. Of the 1,025 which were allowed to be treated at home, 50 per cent died. In October, 1874 a corps of vaccinators was organized, and more than 126,000 individuals were vaccinated. Over $1,200 worth of vaccine was sold to physicians, druggists and health departments outside of the City. Some 24,000 quill points were distributed free of charge to charitable institutions. At the time that the corps was organized, a bill was passed by the Legislature providing for the establishment of a laboratory for the preparation of vaccine virus and for the sale of any surplus. The money received constituted a fund which was used by the Board of Health to promote vaccination.

Diphtheria was prevalent in 1874. The Board of Health prepared and distributed leaflets describing what was then known about the disease. An intensive study of diphtheria was made with special emphasis on its micropathology.

In 1875 following the death of four individuals from hydrophobia, Dr. Charles R. Russell, sanitary inspector, recommended that dogs that bit human beings should not be destroyed immediately but should

be kept under close surveillance until the suspicion of rabies was allayed or confirmed. He suggested further that "valuable and esteemed animals" which may have been in contact with rabid dogs should be kept under observation under suitable conditions for at least six months. Since there was no rabies vaccine in those days, nothing could be done for the person bitten beyond cauterizing the wound.

Because the infant death rate rose sharply during the summer months, a "summer corps" of physicians was organized in 1876 to visit every tenement house; to prescribe for the sick infants; advise on hygienic measures; and distribute leaflets on infant care. In 1879 the State Legislature passed a law requiring the Board of Estimate to appropriate each year the sum of $10,000. This was known as "The Tenement House Fund," and enabled the Health Department to employ this special corps of physicians. This summer corps was in fact the beginning of the Division of Child Hygiene which was to be formally organized as a bureau some thirty years later.

In those days Health Department physicians, who were called sanitary inspectors, had many and varied duties. They investigated tenement houses for defective plumbing, drainage and ventilation; visited cases of smallpox, typhus fever and other contagious diseases; performed vaccinations; and made sanitary surveys. Many of them rose to be leaders in the field of public health.

The first important step in getting a safe milk supply for New York City was the work of Professor Chandler who described the common practice of watering milk. The next step was taken by Ernest J. Lederle, who in 1892 was Acting Chemist.* Lederle seized the milk taken from diseased cows and had it inoculated into guinea pigs. The guinea pigs developed tuberculosis from which they eventually died. This demonstration made a great impression on all public health workers, and convinced any who might still have doubted, of the need for a safe and wholesome milk supply.

In 1896 the Sanitary Code was amended to require a permit from the Board of Health in order to sell milk in this city. Such permits are now recognized as the indispensable basis for the administrative control of a city's milk supply. Six years later orders were issued to a creamery outside city limits to discontinue the practice of removing

* Dr. Lederle became Health Commissioner ten years later, serving from 1902 to 1904. He was reappointed in 1910 and remained in that position until 1914.

cream from milk and adding coloring matter and formaldehyde to it before offering it for sale in New York City. The creamery refused to comply stating that the Department had no jurisdiction outside of the city. The Board of Health called a public hearing at which the milk company was asked to show cause why its permit to sell milk in this city should not be revoked. Following this hearing at which the milk inspectors' report was confirmed, the permit was revoked and the company driven out of business in New York City. After that the authority of the Board of Health in safeguarding milk sold in this city, whether it related to a practice inside or outside the city limits, was firmly established.

Dr. Roger S. Tracy who was Deputy Registrar in 1893, divided the city into sanitary districts when computing his statistics. In this way he was able to secure statistical information regarding health and disease among groups of people of like race and nationality living under similar conditions. This was the forerunner of district health administration.

Until 1880, it was the practice of small towns north of New York City to send their cases of smallpox across the Harlem River into the City. After being apprehended by our Health Department, the patients would be placed in the Riverside Hospital on Blackwell's Island. When the Board of Health realized that the City was being imposed upon in this way, the practice was stopped and Westchester was forced to build a small shack near the East River for the accommodation of its smallpox cases. One of the first persons to be hospitalized in the Westchester shack was a Negro, and when the indignant citizens of the community discovered that he was being "harbored" in their midst, they burned the shack and forced the caretaker and his patient into a boat setting them adrift in the river. These two found refuge on North Brother Island where they took possession of an unoccupied house. This was the beginning of the use of North Brother Island for the housing of patients with contagious diseases. Some years later, a building was erected and all smallpox cases in the city were transferred to it.

In the spring of 1885, a hospital for diphtheria cases was built at the foot of East 16th Street and named for Dr. Willard Parker, Vice-President of the first Metropolitan Board of Health and a leader in public health. A few years later, the City of Brooklyn, having decided to take care of its own cases of contagious disease, purchased property

north of Kings County Hospital for buildings to be used for that purpose.

The discoveries of Pasteur and Koch greatly changed methods of public health administration. Through the work of these scientists and their pupils the true sources of communicable diseases were revealed. No longer was it believed that disease was caused by germs in the atmosphere. Drs. Biggs, Prudden and Loomis, consulting pathologists to the Health Department, were practically the first health authorities to recognize the advent of a new era in medicine. Their recognition was evidenced in 1887 by their report to the Board of Health recommending that tuberculosis be officially declared a communicable disease, and be made reportable. A bulletin of information on tuberculosis was prepared and distributed in the tenement house districts. However, it was not until 1894 that the Board of Health finally accepted the recommendation that tuberculosis be made "a notifiable disease." It was due to Dr. Hermann Biggs' untiring efforts that this essential act in the control of tuberculosis was adopted.

It was in 1892 that the first municipal bacteriological diagnostic laboratory in the world was established by the New York City Department of Health. This also was due to the persistence of Dr. Biggs who for years had asked for the establishment of a division of bacteriology. In that year there was an epidemic of cholera in Hamburg and the danger of its spread to New York was recognized by all. When the members of the Board of Estimate read in the newspapers that five steamships from Hamburg were being detained at Quarantine because of cases of cholera aboard, and that five deaths from that disease had occurred on one of them, they were almost panic-stricken. They gave an attentive ear to any plan for avoiding the threatened pestilence. In that mood they withdrew their opposition towards a laboratory and voted funds for its establishment. Thus in September, 1892 an emergency laboratory for the diagnosis of suspected cases of cholera was opened on the third floor of a building at 42 Bleecker Street. Dr. Hermann M. Biggs was placed in charge and given the title, "Chief of the Division of Pathology, Bacteriology and Disinfection." Similar emergency laboratories had been set up in Hamburg, Bremen, Berlin and London but these were all disbanded after the cholera emergency had passed.

Under the able guidance of Dr. Biggs, the Health Department's laboratory was continued and expanded to become an important part

of the Department's services. Soon after it was opened, Dr. Biggs stated that "the laboratory was to determine the differential diagnosis between follicular tonsillitis and diphtheria; to make scientific investigation in regard to the organisms of cholera, yellow fever, anthrax, etc.; to estimate the number of bacteria in Croton water; to make bacteriological examination of milk, meat and other foods; and to determine the value of different disinfectants."

In April, 1893, Dr. Biggs brought Dr. William H. Park into the laboratory and assigned to him the problem of working out a practical method of aiding physicians in the diagnosis of diphtheria. Park devised the diagnostic outfits for making throat cultures, and with the help of Dr. Biggs organized the system whereby such outfits could be made available in conveniently located drug stores, and collected daily by messenger. In January, 1894, the laboratory began sputum examinations for tubercle bacilli. Sputum bottles were also made available at drug store stations. Among the laboratory procedures that were soon added were examinations for gonococci, for malaria and for typhoid (Widal reaction).

The establishment of this laboratory had an important influence on public health throughout the country, in fact, throughout the world. It was the first municipally owned diagnostic laboratory. It inaugurated procedures which were adopted by other health departments. It stimulated studies which resulted in a great improvement in the laboratory diagnosis of communicable diseases.

News of the good results reported by Von Behring on the use of the antitoxin in the treatment of diphtheria reached New York. Under the sponsorship of the New York Herald a fund was raised for the making of antitoxin and its distribution to diphtheria patients who were unable to pay for it. The fund was turned over to the Department of Health to be expended under the supervision of an advisory committee of eminent physicians including Dr. Biggs and Dr. Park. This was the beginning of New York City's antitoxin laboratory.

In 1895, legislation was enacted authorizing the Department of Health to produce, use and distribute diphtheria antitoxin and other antitoxins and to sell any surplus products. The proceeds from the sales were to be utilized for further studies in the production and use of the various antitoxins. These funds made possible the organization of the Research Division of the Bureau of Laboratories.

As a result of a Tenement House Act passed in 1895, the Health Department's Corps of Sanitary Inspectors was increased. In accordance with the provisions of the new law, two inspections were made of each tenement house in the City. The total number of inspections and reinspections during the year amounted to over 169,000 and resulted in the discovery of some 18,000 violations. At that time, there were nearly 41,500 tenement houses in the City. About 600 of them were ordered vacated by the Board of Health as unfit for human habitation. The order was rescinded in all but 68 cases because the owners of the houses immediately started to make the necessary repairs. The houses that were vacated were either beyond repair or their owners didn't take the Health Department's order seriously. Vigorous action against unfit tenements continued during the following years as the Board felt that "no branch of the sanitary work carried on by this Department is of greater importance to the public health." In 1901 the Tenement House Department was created and jurisdiction over all dwellings housing more than two families was transferred to it.

In 1898 the City of New York added to its territory by the incorporation of the City of Brooklyn and of several neighboring towns and villages. This act was technically called the Consolidation Act. The task then fell upon the Board of Health to acquaint the citizens of the newly added communities with the requirements of the Sanitary Code.

In the report of that year, drug control activities of the Department came to the fore, with particular attention to headache powders containing coal tar derivatives which were sold without prescription, and to "catarrh cures" containing cocaine. Many so-called remedies for drunkenness were found to contain as much alcohol as whiskey. Lead and morphine were among the dangerous ingredients found in other proprietaries. The recommendation was made that all of these deceptions, frauds and dangerous practices be suppressed by law.

Although the Division of Child Hygiene was not established until 1908, school medical inspections began with the appointment of 150 physicians in 1897. They were attached to the Division of Contagious Diseases, and were interested chiefly in the inspection of children who had been ill. In 1902 seventeen public health nurses were assigned to schools to assist the physicians. This was the first time in the history of the United States that nurses were assigned to this kind of work. In 1908, when the Division was finally established and placed under

the direction of Dr. S. Josephine Baker, a pioneer in infant welfare, its functions included: The control and supervision of midwives; the reduction of infant mortality; the supervision of foundlings boarded in private homes; the inspection and sanitary supervision of day nurseries; the inspection of institutions harboring dependent children; the medical inspection and examination of school children; the vaccination of school children; and the enforcement of that part of the Child Labor Law relating to the issuance of employment certificates. Infant milk stations, the forerunner of the child health stations, were set up in 1911. Except that the various functions of this bureau have been extended to meet changing conditions, the organization today is substantially the same as it was when the Division was organized almost forty years ago.

In 1902 and 1903, Drs. Park and Holt did important research on the relation between infant mortality and bacteria in milk. This study showed that cholera infantum, or as it was popularly called "summer diarrhea," was not caused by any specific pathogenic organism, but was due to large numbers of ordinarily harmless bacteria. The delicate mucosa of infants could not withstand their attack. Thus the importance of determining the numbers of bacteria in milk and other foods as well as the kinds of bacteria was clearly demonstrated. In spite of this report it was not until eight years later that the Board of Health added to the Sanitary Code a section requiring the pasteurization of milk offered for sale in New York City.

In 1906 the Health Department extended its milk inspection in a manner that was entirely new for a municipality. Inspectors were sent to farms in New York State and other states where milk was produced for sale in this city. In this way the Department had control of the milk from the time it was produced until it was delivered to the consumer. During the following year, a system of examining and keeping under surveillance all typhoid carriers in New York City was initiated.

Although the Health Department's venereal disease activities were not placed in a separate bureau until 1934, Dr. Hermann M. Biggs initiated a comprehensive anti-venereal disease program in 1912. This embraced: the reporting of syphilis and gonorrhea by private physicians, hospitals and clinics; offering the services of the Health Department's laboratory for Wassermann tests free of charge (gonococcus smears had long been a routine service); establishment of special clinics

for diagnosing and treating venereal diseases (darkfield examinations, and distribution of salvarsan); providing special hospital facilities where irresponsible patients could be forcibly detained until no longer infectious; an educational campaign against patent nostrums and quackery in the treatment of venereal diseases. This pioneer program has served as a model for all the work now carried on in this field throughout the United States.

Biggs looked upon venereal diseases from the point of view of a physician and a public health administrator. Venereal diseases are communicable diseases and it is the duty of the Health Department to use every available means to stamp them out. At Bellevue Hospital where Biggs had a medical service, he ordered routine Wassermann tests on all the patients in his wards. The Department of Health ran a paid newspaper advertisement warning against quacks. Signs bearing similar warnings were put up in the toilet rooms of saloons, restaurants and other public places. Soon after his appointment as Commissioner of Health of the State of New York, Biggs secured the enactment of legislation prohibiting advertising for treatment of venereal diseases throughout the State.

During Dr. Lederle's second term as Commissioner of Health (1910 to 1914) compulsory pasteurization of milk was introduced. The Department of Health was reorganized into eight bureaus: Bureau of General Administration, Bureau of Records, Sanitary Bureau, Bureau of Child Hygiene, Bureau of Infectious Diseases (later named Preventable Diseases), Bureau of Food and Drugs, Bureau of Hospitals and Bureau of Laboratories. In 1914 the Bureau of Health Education was established; in 1928, the Bureau of Nursing.

In 1934 the Bureau of Tuberculosis was set up as a separate unit, and this was followed the next year by the establishment of the Bureau of Social Hygiene. These diseases were considered to be of sufficient importance to warrant this change in administration. Up to that time, they had been under the jurisdiction of the Bureau of Preventable Diseases. In 1929 the contagious disease hospitals including institutions treating tuberculous patients were transferred to the Department of Hospitals. Although the District Health Center program as we know it today began late in Commissioner Shirley W. Wynne's administration, the first experimental health center was set up in New York City in 1915 under the direction of Commissioner S. S. Goldwater.

Approximately ten years ago, a plan was worked out whereby medical students were given practical training in the health centers. This was a logical development of the growing importance of preventive medicine in the medical school curriculum. No public health program can be completely successful without the active participation of all the physicians in the community. The Health Department is, therefore, eager to do all it can to acquaint both medical students and physicians with the public health problems and the means at hand for combating them.

Dr. Linsly R. Williams, who was Managing Director of the National Tuberculosis Association and Director of The New York Academy of Medicine, once said, "Public health is not hygiene or preventive medicine. It is a concept of the conditions of health of the community. Efforts to conserve the public health include both those which affect the health of the community as a whole, and those which seek to prevent any individual or group of persons from affecting adversely the health of others."* The last part of that statement is especially noteworthy today when the Health Department is making every effort to have food establishments operate in compliance with the provisions of the Sanitary Code. An ignorant or careless food handler is a definite health hazard. The owner is responsible for operating a food establishment in accordance with high sanitary standards, and the Health Department is determined that he be made to understand and fully meet that obligation.

In conclusion, it might be interesting to compare the health problems confronting us today with those faced by public health officers eighty years ago. Pestilence has been conquered. No longer are yellow fever, cholera, typhus and smallpox major health problems in New York City. The common communicable diseases that annually took the lives of thousands of children have been brought under control. The life expectancy at birth has increased from about 31 years in 1880 to over 65 now. Today increasing attention must be given to the diseases of later life. Public health officials, no less than physicians and social workers, must recognize their responsibility for making the added years gained through the saving of lives in the younger age groups, more healthful and more enjoyable. There must of course be no lessening of effort in the fight against communicable disease, but this

* "Role of Practitioners in Modern Public Health Work."—Preventive Medicine and Public Health, Thomas Nelson and Sons, New York—1928.

fight must be extended to include the diseases that are more prevalent among the elderly, namely, diabetes, cancer, diseases of the heart, blood vessels and kidneys.

We in the New York City Health Department feel certain that we will continue to have the wholehearted coöperation of the physicians practicing in this city. Were it not for their unselfish and untiring efforts throughout the years the story would have been quite different. Many of the great advances that have been made in improving the public health would probably never have been recorded. Special mention should be made of the many helpful suggestions given to the Department of Health by the Committee on Public Health Relations of The New York Academy of Medicine.

The Health Department has had a distinguished history. Not one or two but a host of outstanding men and women have been associated with it, and have produced methods and techniques that have become standard for health departments throughout the world. Those of us who are charged with the responsibility of protecting the public health today hope that we, like our predecessors, can overcome the obstacles of ignorance, superstition, prejudice and apathy; that we shall not falter in the job ahead, but that we may be enabled to carry on in the tradition of those who traveled the road before us.

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Victor Robinson
1886-1947

The conventional obituary of Victor Robinson will give the facts of his life, detail his literary contributions, and the titles awarded him by schools and universities. A personal note may not be amiss.

Close to a quarter century ago, because of a short historical note submitted to him as editor of Medical Life, Victor Robinson invited me to his offices on Mount Morris Park, West. Victor Robinson was an intense person, then. He remained an intense person for his life time. He radiated intensity of purpose and intensity of ideals. He became enthusiastic in the presence of one entering the portals of history of medicine. He welcomed each worker striving to unveil the influences of the past in medicine and culture upon the current scene. His own studies encompassed all the specialties of medicine and surgery; of dentistry; and of nursing. He knew the basic and the accessory facts regarding each group from earliest to modern times. The nature of Victor Robinson caused him to accept the offerings of each as if they were truly spectacular and earth-rocking in importance. He cherished each item as if it were the key to the entire historical structure.

Victor Robinson accumulated a store of information on the things that were and are not alone from books, but from experience. He made on the site investigations. He visited and revisited the cradles of our medical heritage. He relived the life of each of his hundreds of heroes. He seemed actually to have cast himself into the period, into the thinking of each epoch. Dr. Robinson surrounded himself with the memories of the person, with his home, his family, his politics. He came to know the streets he trod; yes, the very cobbler responsible for the sandals or the shoes or the boots each wore on his daily route from home to market place, to school. He suffered the tortures of each truthsayer bound to the fiery stake. He was elated with each honor heaped upon the chosen.

Victor Robinson had an astounding memory. He forgot nothing. He recalled minute things and dates and places and titles and books—especially books. He could discourse for hours on end at formal or informal lecture meetings on individuals or entire movements without one glance at a card or a paper. He conducted his classes without notes. His flow of language in speech and in writing was superb. His references covered the earth, and included each decade of man's residence here. His quotations were apt. How easy it is to say: Victor Robinson was a scholar.

Yes, Victor was a scholar, but he was no cloistered scholar. He knew the world about him. He felt the impress of each social change. He travelled to far distant places to gain his own impressions of these changes.

Perhaps the greatest measure of the man, for those outside his immediate family, was his capacity for friendship. He always found a moment to share with people. He never said an ill word of anyone. He accepted tasks from friends and from acquaintances. He read manuscripts for people he scarcely knew. He made helpful suggestions. He corrected errors. He softened harsh criticism. He gave freely of his time, his energies, and his knowledge. He accepted the teaching post and the professorship in medical history at Temple University in Philadelphia in 1929. He continued to teach, indeed increased the number of his courses although this required he awaken at five in the morning on Wednesday of each week of the academic year and travel to Philadelphia. He received no honorarium. He accepted no recompense other than the enthusiasms of his pupils. He taught medical students, and nursing pupils from the training schools of Philadelphia hospitals, denominational and otherwise. He conveyed his thoughts to eager groups. He felt lifted by their acceptance of his lecture and illustrative material.

Much regarding Victor Robinson re-

mained his very own. He never burdened friends with his difficulties or troubles. He never wore his heart on his sleeve. The days never seemed long enough for work and study. There were not enough evenings for discourse with friends. There never was enough time for gaiety. One can never forget those evenings at home at Mount Morris Park West of a decade ago. One was never certain what was to happen next. A singer from a stranded Italian opera company would give a concert right there; or an entire troupe would entertain. A musician lost in our land from Russia would find the piano. A scholar recently arrived from Holland would have a group in one corner of one of the rooms on one of the floors of the house. A painter with the ylang-ylang of the Parisian subway still clinging to his clothes would enthuse over the animated talk of an art student. A playright, a public relations counsel, a book publisher, a highly rated specialist and a family physician, a down at the heel translator from the German—these would rub shoulders at an evening at the Robinson's. Food and drink in abundance and talk in half a dozen languages at one time.

But best of all, one recalls Victor Robinson at his desk. Short, lean, he was at his desk ever piled high with reference books, dictionaries, biographies, galley proof, manuscript, editorial scissors, blue pencils. Victor with his glasses high on his forehead peering, ever peering at the word. He did so much, and had wished to do so much more. Two new books reached the stores about the time of his sixtieth birthday. His friends had submitted material for a Festschrift—some sixty articles had been contributed on medical historical topics. The publication must wait now. It will be a memorial to Victor Robinson from his friends and co-workers in a field whose importance is ever increasing.

Many years ago, Victor Robinson wrote: "Interest in the History of Medicine has persisted, for it is the greatest of stories—the record of man's conflict with credulity."

HERMAN GOODMAN

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("Possession does not imply approval.")

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